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Health and Environmental Effects Document for Bromochloromethane

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Health and Environmental Effects Documents (HEEDS) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference Doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. In the case of suspected carcinogens, RfDs may not be estimated. Instead, a carcinogenic potency factor, or q_1^*, is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA.

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HEALTH AND ENVIRONMENTAL EFFECTS DOCUMENT FOR BROMOCHLOROMETHANE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Documents (HEEDs) are prepared for the Office of Solid Waste and Emergency Response (OSWER). This document series is intended to support listings under the Resource Conservation and Recovery Act (RCRA) as well as to provide health-related limits and goals for emergency and remedial actions under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained for Agency Program Office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched for in this document and the dates searched are included in "Appendix: Literature Searched." Literature search material is current up to 8 months previous to the final draft date listed on the front cover. Final draft document dates (front cover) reflect the date the document is sent to the Program Officer (OSWER).

Several quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include: Reference doses (RfDs) for chronic and subchronic exposures for both the inhalation and oral exposures. The subchronic or partial lifetime RfD, is an estimate of an exposure level which would not be expected to cause adverse effects when exposure occurs during a limited time interval i.e., for an interval which does not constitute a significant portion of the lifespan. This type of exposure estimate has not been extensively used, or rigorously defined as previous risk assessment efforts have focused primarily on lifetime exposure scenarios. Animal data used for subchronic estimates generally reflect exposure durations of 30-90 days. The general methodology for estimating subchronic RfDs is the same as traditionally employed for chronic estimates, except that subchronic data are utilized when available.

In the case of suspected carcinogens, a carcinogenic potency factor, or q_1^* (U.S. EPA, 1980), is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively. An RfD may also be derived for the noncarcinogenic health effects of compounds that are also carcinogenic.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity, and acute mammalian toxicity). Chemical-specific RQs reflect the lowest of these six primary criteria. The methodology for chronic toxicity and cancer based RQs are defined in U.S. EPA, 1984 and 1986a, respectively.

EXECUTIVE SUMMARY

Bromochloromethane is a clear, colorless liquid with a sweet odor (Stenger, 1978). It is completely miscible with most common organic solvents (Stenger, 1978) and soluble in water to the extent of 16.7 g/ℓ at 25°C (Tewari et al., 1982). Current production figures are not available. Recent manufacturers of bromochloromethane include Dow Chemical and Ethyl Corporation (USITC, 1988; SRI, 1989). Bromochloromethane is used mainly as a fire-extinguisher fluid in aircraft and portable extinguishers (Stenger, 1978). It is also used in chemical synthesis (Kuney, 1988).

Bromochloromethane is expected to degrade relatively slowly in the atmosphere. Using the method of Atkinson (1987), the half-life with respect to HO• reaction can be estimated at ~168 days. This suggests that ~2% of tropospheric bromochloromethane will diffuse into the stratosphere and be destroyed by direct photolysis. Physical removal from the atmosphere by wet deposition may be possible, but its relative significance is not known. A single biodegradation study (Tabak et al., 1981) suggested that biodegradation of bromochloromethane is an important environmental fate process. Volatilization from water and soil surfaces is a major fate process. Volatilization half-lives of 4 and 47 hours were estimated for a model river (1 m deep) and for an environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986b). Bromochloromethane may leach readily in soils, based upon an estimated K_{oc} value of 21 (Swann et al., 1983). Aquatic hydrolysis is not environmentally significant (Mabey and Mill, 1978).

Bromochloromethane has been detected in drinking water (Suffet et al., 1980; Lucas, 1984), groundwater (Zoeteman et al., 1981), Lake Ontario and Niagara River water (1-10 ng/ℓ) (Kaiser et al., 1983) and open seawater from the Atlantic Ocean (0.02 ng/ℓ) (Class and Ballschmiter, 1988).

Levels of 0.2-0.4 ppt have been identified in air over the Atlantic Ocean (Class and Ballschmiter, 1988), while levels of 2.4-2.9 ppt were detected in the Alaskan Arctic (Rasmussen and Khalil, 1984). Bromochloromethane has also been identified in air samples collected near a hazardous waste site in New Jersey (Laregina et al., 1986). It has been suggested that the presence of bromochloromethane in marine water and air may be due, in part, to its biogenic formation in algae, followed by release to seawater, with subsequent volatilization (Class and Ballschmiter, 1988). The classic haloform reactions responsible for the formation of chloroform and other halomethanes during chlorination of drinking water will not produce bromochloromethane (NAS, 1980).

Summarized toxicity data for bromochloromethane consisted of a NOEL of 80 mg/ℓ for fathead minnows, P. promelas, and an LC_{50} (duration not reported) of ≥80 mg/ℓ (U.S. EPA, 1987). Bromochloromethane has been found in tissues of rainbow trout, S. gairdneri, from the Colorado River. The estimated whole-fish concentration was 8 µg/ℓ (Hiatt, 1983).

Bromochloromethane is rapidly absorbed by rats in a biphasic manner following acute inhalation exposure (Gargas and Andersen, 1982), but quantitative data are not available regarding the extent of inhalation exposure or the rate or extent of oral exposure. There appears to be some distribution of bromide to the brain of dogs during subchronic inhalation exposure (Svirbely et al., 1947). Rat tissue:blood partition coefficients (Gargas et al., 1986a,b) suggest that bromochloromethane will distribute more readily to fat than to liver or muscle. Available data indicate that bromochloromethane is metabolized by two major pathways: an oxidative, cytochrome P-450 mediated pathway yielding CO and halide by putative formyl halide intermediates, and a glutathione (GSH)-dependent cytosolic pathway producing

CO_2 and halide (Gargas et al., 1986a). It is proposed that a portion of the oxidative pathway also yields a significant amount of CO_2 (Gargas et al.,1986a). Information regarding the rate and extent of bromochloromethane excretion was not located in the literature cited in Appendix A.

Acute inhalation LC_{50}s for mice for 7-hour exposures ranged from 2268-2995 ppm (Svirbely et al., 1947; Highman et al., 1948). Exposure to 5000 ppm (26,460 mg/m³) for 7 hours was not lethal for rats (Torkelson et al., 1960). Rats survived a single oral dose of 5 g/kg, and all rats died within 24 hours after a dose of 7 g/kg (Torkelson et al., 1960). An oral LD_{50} of ~4300 mg/kg was determined for mice (Svirbely et al., 1947). Signs and pathological effects of acute inhalation and oral exposure to bromochloromethane are similar; principal effects include CNS depression and degeneration of the liver.

Subchronic inhalation studies of bromochloromethane have been conducted with rats, mice, guinea pigs, rabbits and dogs (Torkelson et al., 1960; MacEwen et al., 1966; Svirbely et al., 1947; Highman et al., 1948). Concentrations ranged from 370 ppm (rats) to ~1000 ppm (all species); exposures were usually 5-7 hours/day, 5 days/week ranging from 14 weeks to ~6 months. Generally, minor effects such as decreased body weight, increased relative liver and kidney weight and reversible liver and kidney histological alterations occurred at concentrations $\geq$500 ppm in most species. Torkelson et al. (1960) found that relative liver weight was increased in rats at concentrations of 370 ppm with histological effects occurring at 490 ppm. Exposure to 1000 ppm caused death and marked liver injury in mice (Highman et al., 1948). Information regarding the chronic inhalation toxicity, subchronic or chronic oral toxicity or teratogenicity of bromochloromethane were not located. Decreased spermatogenesis and fibrosis occurred in the tubules of

the testes of guinea pigs and rabbits that were subchronically exposed to ~1000 ppm bromochloromethane by inhalation (Torkelson et al., 1960). The functional significance of these effects was not evaluated.

Pertinent information regarding the chronic inhalation and oral exposure of human or animals to bromochloromethane were not located in the available literature cited in Appendix A.

The carcinogenicity of bromochloromethane has not been evaluated. Bromochloromethane was mutagenic in Salmonella typhimurium and Escherichia coli bacteria (Simmon, 1976; Simmon et al., 1977; Osterman-Golkar et al. 1983; Strobel and Grummt, 1987) and induced SCE and chromosome aberrations in Chinese hamster cells in vitro (Strobel and Grummt, 1987).

An RfD for subchronic inhalation exposure of 4 mg/m³ was based on a NOAEL associated with slightly elevated liver weight but no effect on body weight in female rats exposed intermittently for 195 days (Torkelson et al., 1960). This study also served as the basis for an RfD of 0.4 mg/m³ for chronic inhalation exposure. Oral data were not sufficient for deriving route-specific RfD values; therefore, the NOAEL from the inhalation study in female rats by Torkelson et al. (1960) served as the basis for an RfD of 1 mg/kg/day for subchronic oral exposure and an RfD of 0.1 mg/kg/day for chronic oral exposure. An RQ for noncancer chronic toxicity of 1000 was based on the occurrence of liver lesions in rats exposed by inhalation for 114 days.

Bromochloromethane is classified in EPA Cancer Group D (Not Classifiable as to Human Carcinogenicity) because of lack of carcinogenicity data; this lack of data precludes calculation of a carcinogenic potency factor or cancer-based RQ for bromochloromethane.

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LIST OF ABBREVIATIONS

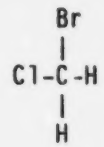
AEL	Adverse-effect level
A/G	Albumin/globulin
CAS	Chemical Abstract Service
CNS	Central nervous system
CO	Carbon monoxide
CO_2	Carbon dioxide
CS	Composite score
DWEL	Drinking water equivalent level
FEL	Frank-effect level
GSH	Reduced glutathione
HA	Health advisory
HEC	Human equivalent concentration
HED	Highest effective dose
Km	Concentration in air at which uptake occurs at one-half the maximum rate
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration levels)
LD_{50}	Dose lethal to 50% of recipients
LDU	Log dose units
LED	Lowest effective dose
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level

PEL	Permissible exposure limit
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*
STEL	Short-term exposure limit
TLV	Threshold limit value
TLV-STEL	Threshold limit value-Short-term exposure limit
TWA	Time-weighted average
UV	Ultraviolet
V_{max}	Maximum rate of uptake

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Bromochloromethane is the common name for the chemical known by the synonyms chlorobromomethane, methylene chlorobromide, fluorocarbon 1011 and Halon 1011 (Chemline, 1989). The structure, molecular weight, empirical formula and CAS Registry number for bromochloromethane are as follows:



Molecular weight: 129.39

Empirical formula: CH_2BrCl

CAS Registry number: 74-97-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Bromochloromethane is a clear, colorless liquid with a sweet odor (Stenger, 1978). It is completely miscible with most common organic solvents. Selected physical properties of bromochloromethane are as follows:

Melting point:	-87.95°C	Riddick et al., 1986
Boiling point:	68.06°C	Riddick et al., 1986
Density (25°C):	1.923 g/cm³	Riddick et al., 1986
Water solubility at 25°C:	16.7 g/ℓ	Tewari et al., 1982
Vapor pressure at 25°C:	147.2 mm Hg	Riddick et al., 1986
at 15.72°C:	93.34 mm Hg	McDonald et al., 1959
Log K_{ow}:	1.41	Tewari et al., 1982
Air odor threshold:	400 ppm	Amoore and Hautala, 1983
Water odor threshold:	200 ppm	Amoore and Hautala, 1983

Bromochloromethane is nonflammable and does not have a flash point (Hawley, 1981; Dean, 1985).

1.3. PRODUCTION DATA

Recent production figures for bromochloromethane are not available. The public portion of the U.S. EPA TSCA Production File for 1977 lists Dow Chemical (Midland, MI) as a manufacturer of 1-10 million pounds and Bruckman Laboratories, Inc. (Memphis, TN) as a manufacturer of 10-100 thousand pounds (U.S. EPA, 1977).

The 1989 Directory of Chemical Producers (SRI, 1989) lists Ethyl Corporation (Magnolia, AK) as a current manufacturer of bromochloromethane. USITC (1988) lists Dow Chemical as a manufacturer during 1987.

Bromochloromethane is prepared by reacting dichloromethane with anhydrous aluminum bromide (treatment with bromine and aluminum) or by reaction with hydrogen bromide in the presence of an aluminum halide catalyst, followed by water washing and distillation (Stenger, 1978).

1.4. USE DATA

Bromochloromethane is used mainly as a fire-extinguisher fluid in aircraft and portable extinguishers (Stenger, 1978). It is also used in chemical synthesis (Kuney, 1988).

1.5. SUMMARY

Bromochloromethane is a clear, colorless liquid with a sweet odor (Stenger, 1978). It is completely miscible with most common organic solvents (Stenger, 1978) and soluble in water to the extent of 16.7 g/ℓ at 25°C (Tewari et al., 1982). Current production figures are not available. Recent manufacturers of bromochloromethane include Dow Chemical and Ethyl Corporation (USITC, 1988; SRI, 1989). Bromochloromethane is used mainly as a fire-extinguisher fluid in aircraft and portable extinguishers (Stenger, 1978). It is also used in chemical synthesis (Kuney, 1988).

2. ENVIRONMENTAL FATE AND TRANSPORT

2.1. AIR

The relatively high vapor pressure of bromochloromethane (147.2 mm Hg at 25°C) indicates that it probably exists almost entirely in the vapor phase in the ambient atmosphere (Eisenreich et al., 1981). Using the method of Atkinson (1987), the rate constant for the vapor-phase reaction of bromochloromethane with atmospheric HO• can be estimated at 9.55×10^{-14} cm^3/molecule-sec at 25°C. This rate constant corresponds to a half-life of ~168 days, assuming an average atmospheric HO• concentration of 5×10^5 molecules/cm^3.

Bromochloromethane does not absorb UV light at >290 nm (Cadman and Simons, 1966). Therefore, direct photolysis will not occur in the troposphere. However, the relatively long half-life predicted for reaction with HO• suggests that some bromochloromethane may eventually diffuse into the stratosphere, where direct photolysis can destroy the compound. Based on a half-life of 168 days and a tropospheric-to-stratospheric turnover time of 30 years, ~2% of tropospheric bromochloromethane will diffuse into the stratosphere.

Pertinent data regarding the physical removal of bromochloromethane from the atmosphere were not located in the literature cited in Appendix A. Bromochloromethane's water solubility of 16,700 mg/ℓ at 25°C (Iewari et al., 1982) suggests that physical removal by wet deposition (rainfall, dissolution into clouds, etc.) is possible. However, the significance of physical removal cannot be verified because of lack of experimental data.

2.2. WATER

2.2.1. Hydrolysis. The hydrolysis half-life of bromochloromethane has been estimated at ~44 years at 25°C and pH 7 (Mabey and Mill, 1978). Therefore, hydrolysis is not environmentally significant.

2.2.2. **Photolysis.** UV spectra, as determined by Cadman and Simons (1966), predict that direct photolysis of bromochloromethane has no significance in the environment since no absorption occurs at >290 nm.

2.2.3. **Microbial Degradation.** Tabak et al. (1981) studied the biodegradability of 114 organic priority pollutants on the U.S. EPA Priority Pollutants List to ascertain microbial degradation and acclimation periods. The Bunch and Chambers static culture flask biodegradability screening test was performed under a set of controlled experimental conditions that included the following parameters: 5 and 10 mg/ℓ concentrations of the test compound, 5 mg/ℓ of yeast extract in the synthetic medium, 7-day static incubation at 25°C in the dark followed by three weekly subcultures (totaling 28 days of incubation), and incorporation of settled domestic wastewater as the microbial inoculum. With respect to bromochloromethane, 100% loss of compound was observed after the first 7-day inoculation period and after each subsequent subculture. The results indicated significant biodegradation with rapid adaptation.

2.2.4. **Volatilization.** Based upon a water solubility of 16,700 mg/ℓ and a vapor pressure of 147.2 mm Hg at 25°C (see Section 1.2.), the Henry's Law constant for bromochloromethane can be estimated to be 0.0015 atm-m³/mol. A Henry's Law constant of this magnitude indicates that volatilization from environmental waters may be significant and rapid (Thomas, 1982). Using a model river estimation method (Thomas, 1982), the volatilization half-life of bromochloromethane from a river 1 m deep flowing 1 m/sec with a wind velocity of 3 m/sec is ~4 hours. The estimated volatilization half-life from a model environmental pond is ~47 hours (U.S. EPA, 1986b). These estimates indicate that volatilization is a significant environmental fate process for bromochloromethane.

2.2.5. **Adsorption.** K_{oc} estimates presented in Section 2.3.1. predict that bromochloromethane is not tightly bound to soil through adsorption. Therefore, it is likely that adsorption of bromochloromethane in sediments does not compete with volatilization or biodegradation in the disappearance of bromochloromethane from the aquatic environment.

2.3. SOIL

2.3.1. **Adsorption/Leaching.** Pertinent data regarding the leaching of bromochloromethane in soil were not located in the available literature cited in Appendix A. A K_{oc} value of 21 can be estimated using a water solubility of 16,700 mg/ℓ and the following regression-derived equation (Lyman, 1982): $\log K_{oc} = 3.64 - 0.55 \cdot \log$ (water solubility). This K_{oc} value indicates very high soil mobility (Swann et al., 1983).

2.3.2. **Microbial Degradation.** Pertinent data regarding the microbial degradation of bromochloromethane in soil were not located in the available literature cited in Appendix A. The biodegradation results of Tabak et al. (1981) discussed in Section 2.2.3. suggest that biodegradation of bromochloromethane in soil may be significant. Since no other processes are expected to degrade bromochloromethane in soil to a significant degree, biodegradation is probably the ultimate degradation process, although the degradation rate of this process cannot be quantified.

2.3.3. **Volatilization.** The relatively high vapor pressure of bromochloromethane (147.2 mm Hg at 25°C) suggests significant evaporation from dry surfaces. In moist soils, evaporation may still be significant near soil surfaces, although leaching may diminish the relative significance of volatilization.

2.4. SUMMARY

Bromochloromethane is expected to degrade relatively slowly in the atmosphere. Using the method of Atkinson (1987), the half-life with respect to HO• reaction can be estimated at ~168 days. This suggests that ~2% of tropospheric bromochloromethane will diffuse into the stratosphere and be destroyed by direct photolysis. Physical removal from the atmosphere by wet deposition may be possible, but its relative significance is not known. A single biodegradation study (Tabak et al., 1981) suggested that biodegradation of bromochloromethane is an important environmental fate process. Volatilization from water and soil surfaces is a major fate process. Volatilization half-lives of 4 and 47 hours were estimated for a model river (1 m . p) and for an environmental pond, respectively (Thomas, 1982; U.S. EPA, 1986b). Bromochloromethane may leach readily in soils, based upon an estimated K_{oc} value of 21 (Swann et al., 1983). Aquatic hydrolysis is not environmentally significant (Mabey and Mill, 1978).

3. EXPOSURE

3.1. WATER

Bromochloromethane was tentatively identified in a drinking water sample collected in Philadelphia, PA, in August 1976, and in drinking water concentrates collected from New Orleans, LA, in January 1976 (Suffet et al., 1980; Lucas, 1984).

Kaiser et al. (1983) collected water samples from 95 stations on Lake Ontario and 16 stations on the lower Niagara River in 1981 for analysis of volatile halocarbons. Bromochloromethane was detected in one sample at a level of 10 ng/ℓ and in 14 samples at trace levels (detection limit equals 1 ng/ℓ).

Bromochloromethane was qualitatively detected in seawater collected from the Narragansett Bay, RI, in 1979-1980 (Wakeham et al., 1983). Monitoring of the north and south Atlantic Ocean in 1985 yielded a baseline bromochloromethane concentration of 0.02 ng/ℓ (Class and Ballschmiter, 1988). These investigators detected the biogenic presence of bromochloromethane in specific algae that occur in the Atlantic Ocean, and suggested that the occurrence of bromochloromethane in marine water and air may result, in part, from biological emissions from these algae.

Zoeteman et al. (1981) detected a bromochloromethane concentration of 8 µg/ℓ in a contaminated groundwater sample from the Netherlands.

Halomethanes, such as bromodichloromethane, chlorodibromomethane and trihalomethanes, have been detected in drinking waters and other waters during chlorination (Allgeier et al., 1980; Arguello et al., 1979; Dore et al., 1982; Gould et al., 1983). Although bromination can occur when natural bromide is present in the water, the classic haloform reactions responsible for the formation of chloroform and other halomethanes during chlorination will not produce bromochloromethane (NAS, 1980).

3.2. FOOD

Pertinent data regarding the food monitoring of bromochloromethane were not located in the available literature cited in Appendix A.

3.3. INHALATION

The average concentrations of bromochloromethane in ambient air monitored throughout 1983 near Point Barrow, AL (in the Arctic) were 2.4-2.9 ppt (Rasmussen and Khalil, 1984). The higher concentrations were found in the winter and spring when the Arctic haze was observed. The authors suggested that the bromochloromethane in the Arctic air was primarily due to transport from anthropogenic sources. Experimental evidence to support this was not given.

Bromochloromethane was identified (detection limit of 0.1 ppb) in ambient air samples collected near a hazardous waste site in New Jersey (Laregina et al., 1986). The actual concentrations in the samples were not reported.

Mean bromochloromethane concentrations of 0.2-0.4 ppt were measured in the air over the open Atlantic Ocean (30°S-40°N) during monitoring in 1985 (Class and Ballschmiter, 1988). Bromochloromethane was also detected in open seawater and in macro algae collected near various sampling sites. The presence of bromochloromethane in marine air may be due, in part, to its biogenic formation in algae, followed by release to seawater, with subsequent volatilization. Monitoring of baseline concentrations in seawater and air tend to support this supposition.

3.4. DERMAL

Pertinent data regarding the dermal monitoring of bromochloromethane were not located in the available literature cited in Appendix A.

3.5. SUMMARY

Bromochloromethane has been detected in drinking water (Suffet et al., 1980; Lucas, 1984), groundwater (Zoeteman et al., 1981), Lake Ontario and Niagara River water (1-10 ng/ℓ) (Kaiser et al., 1983), and open seawater from the Atlantic Ocean (0.02 ng/ℓ) (Class and Ballschmiter, 1988). Levels of 0.2-0.4 ppt have been identified in air over the Atlantic Ocean (Class and Ballschmiter, 1988), while levels of 2.4-2.9 ppt were detected in the Alaskan Arctic (Rasmussen and Khalil, 1984). Bromochloromethane has also been identified in air samples collected near a hazardous waste site in New Jersey (Laregina et al., 1986). It has been suggested that the presence of bromochloromethane in marine water and air may be due, in part, to its biogenic formation in algae, followed by release to seawater, with subsequent volatilization (Class and Ballschmiter, 1988). The classic haloform reactions responsible for the formation of chloroform and other halomethanes during chlorination of drinking water will not produce bromochloromethane (NAS, 1980).

4. ENVIRONMENTAL TOXICOLOGY

4.1. AQUATIC TOXICOLOGY

4.1.1. Acute Toxic Effects on Fauna. U.S. EPA (1987) summarized results of acute toxicity tests conducted by Dow Chemical Company. No effects were noted in fathead minnows, Pimephales promelas, exposed to 80 mg/ℓ bromochloromethane. The LC_{50} (duration not reported) for this species was ≥80 mg/ℓ. No study details were provided.

4.1.2. Chronic Effects on Fauna.

4.1.2.1. TOXICITY -- Pertinent data regarding the effects of chronic exposure of aquatic fauna to bromochlormethane were not located in the available literature cited in Appendix A.

4.1.2.2. BIOACCUMULATION/BIOCONCENTRATION -- Hiatt (1983) detected the presence of bromochloromethane in tissues of rainbow trout, Salmonella gairdneri, collected from the Colorado River and reported an estimated whole-fish concentration of 8 µg/ℓ.

4.1.3. Effects on Flora.

4.1.3.1. TOXICITY -- Pertinent data regarding the toxic effects of exposure of aquatic flora to bromochloromethane were not located in the available literature cited in Appendix A.

4.1.3.2. BIOCONCENTRATION -- Pertinent data regarding the bioconcentration potential of bromochloromethane in aquatic flora were not located in the available literature cited in Appendix A.

4.1.4. Effects on Bacteria. Pertinent data regarding the effects of exposure of aquatic bacteria to bromochloromethane were not located in the available literature cited in Appendix A.

4.2. TERRESTRIAL TOXICOLOGY

4.2.1. Effects on Fauna. Pertinent data regarding the effects of exposure of terrestrial fauna to bromochloromethane were not located in the available literature cited in Appendix A.

4.2.2. Effects on Flora. Pertinent data regarding the effects of exposure of terrestrial flora to bromochloromethane were not located in the available literature cited in Appendix A.

4.3. FIELD STUDIES

Pertinent data regarding the effects of bromochloromethane on flora and fauna in the field were not located in the available literature cited in Appendix A.

4.4. AQUATIC RISK ASSESSMENT

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to bromochloromethane precluded the development of a freshwater criterion by the method of U.S. EPA/OWRS (1986). Data required for the development of a freshwater criterion include the results of acute assays with a salmonid fish species, a warmwater fish species, a third fish species or an amphibian, planktonic and benthic crustaceans, an insect, a nonarthropod and nonchordate species and an insect or species from a phylum not previously represented. The development of a freshwater criterion will also require data from chronic toxicity tests with two species of fauna and one species of algae or vascular plant and at least one bioconcentration study.

The lack of pertinent data regarding the effects of exposure of aquatic fauna and flora to bromochloromethane prevented the development of a saltwater criterion by the method of U.S. EPA/OWRS (1986). Data required for the development of a saltwater criterion include the results of acute assays with two chordate species, a nonarthropod and nonchordate species, a mysid

or panaeid crustacean, two additional nonchordate species and one other species of marine fauna. The development of a saltwater criterion will also require data from chronic toxicity tests with two species of fauna and one species of algae or vascular plant and at least one bioconcentration study.

4.5. SUMMARY

Summarized toxicity data for bromochloromethane consisted of a NOEL of 80 mg/ℓ for fathead minnows, P. promelas, and an LC_{50} (duration not reported) of ≥80 mg/ℓ (U.S. EPA, 1987). Bromochloromethane has been found in tissues of rainbow trout, S. gairdneri, from the Colorado River. The estimated whole-fish concentration was 8 µg/ℓ (Hiatt, 1983).

5. PHARMACOKINETICS

5.1. ABSORPTION

Male F344 rats were exposed to nine initial concentrations of 100-10,000 ppm (529-52,920 mg/m³) bromochloromethane vapor for 175-205 minutes in a closed inhalation chamber (Gargas and Andersen, 1982). Chamber concentration disappearance curves indicated that absorption was biphasic, consisting of a rapid equilibrium phase that was completed in 70-110 minutes and a slow phase that was nearly linear after this time. The rapid uptake phase reportedly represents initial blood:gas equilibrium. The slow uptake phase, reportedly representing metabolism and loading into poorly perfused tissues, was a composite of a saturable process, which predominated at low concentrations, and a first-order process. Kinetic constants were determined for the saturable process; these included a K_m of 91 ppm (482 mg/m³) and a V_{max} of 10.5 mg/kg/hour. Similar data were reported in other studies (Andersen et al., 1980; Gargas and Anderson, 1982). Gargas et al. (1986a,b) simulated the mixed uptake kinetics of bromochloromethane in rats, using a physiologically-based pharmacokinetic model. Information regarding the extent of respiratory absorption from inhaled bromochloromethane was not located in the available literature.

Quantitative oral absorption data were not located for bromochloromethane. The occurrence of systemic effects in rats and mice following acute oral exposure to bromochloromethane (Section 6.1.3.) provides qualitative evidence of gastrointestinal absorption.

Male F344 rats were exposed to 2500-40,000 ppm (13,230-211,681 mg/m³) bromochloromethane in air for 4 hours in dermal vapor absorption chambers without significant inhalation exposure (McDougal et al., 1985). Blood concentrations of bromide showed that absorption of bromochloromethane was

rapid and increased with increasing exposure levels; however, the increase was not linear. A dermal flux of 0.011-0.164 [illegible]/cm²/hour was calculated.

5.2. DISTRIBUTION

Svirbely et al. (1947) exposed 20 male rats, 3 male rabbits and 2 female dogs (strains not specified) to ~890 ppm (4710 mg/m³) bromochloromethane for 7 hours/day, 5 days/week for 14 weeks. Both total and organic (volatile) bromide were elevated in the blood and brain of the treated animals, compared with unexposed controls, following the last 7-hour exposure. Levels of total bromide in the blood were 6-8 times greater than levels in the brain. Similarly, levels of organic bromide in the blood were 8-12 times greater than levels in the brain.

Rat blood:air and rat tissue:blood partition coefficients for bromochloromethane have been determined as follows: blood:air (41.5±0.9), fat:blood (325±3), liver:blood (29.2±0.5) and muscle:blood (11.1±1.8).

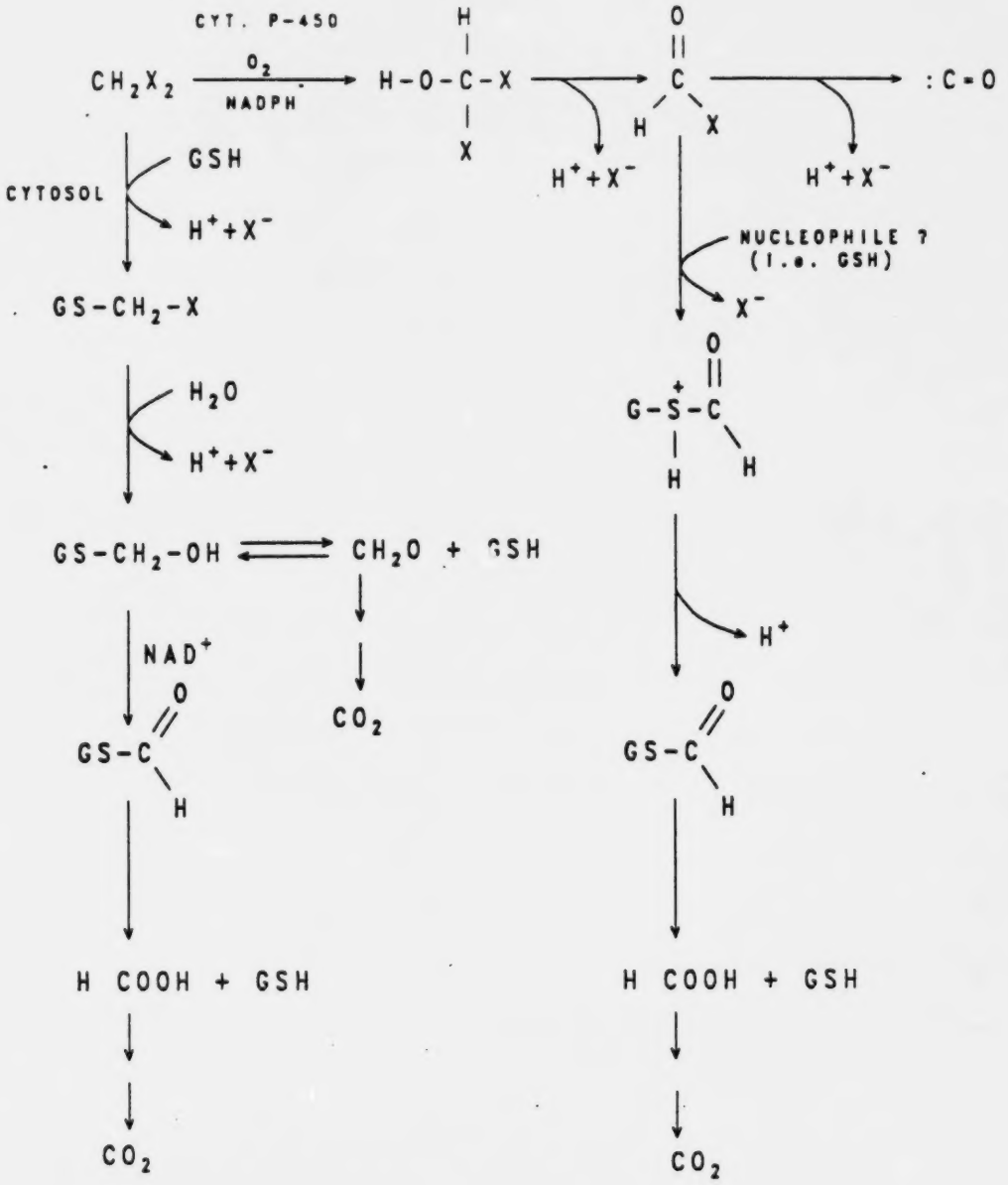
Pertinent data regarding the distribution of bromochloromethane following oral exposure were not located in the available literature cited in Appendix A.

5.3. METABOLISM

Concentrations of inorganic bromide increased in the blood of rats, guinea pigs, rabbits and dogs as a result of subchronic inhalation exposure to bromochloromethane (Svirbely et al., 1947; Torkelson et al., 1960; MacEwen et al., 1966) (Section 6.1.1.1.). Carboxyhemoglobin levels increased in male Long-Evans rats given a single intraperitoneal injection of 3.0 mmol ^{14}C-bromochloromethane/kg (388.2 mg/kg) in corn oil (Kubic et al., 1974). These data and studies of other dihalomethanes indicate that bromochloromethane is metabolized by two major pathways: an oxidative, cytochrome P-450 mediated pathway yielding CO and halide using putative

formyl halide intermediates, and a glutathione-dependent cytosolic pathway producing CO_2 and halide (Gargas et al., 1986a). Based on physiological pharmacokinetic analysis of plasma bromide and carboxyhemoglobin concentrations in rats pretreated with pyrazole (which inhibits microsomal oxidation) and 2,3-epoxypropanol (which depletes glutathione) and exposed to bromochloromethane by inhalation, Gargas et al. (1986a) concluded that bromide was the preferred leaving group in the oxidative mechanism, resulting in the formation of formyl chloride rather than formyl bromide. They proposed that a significant portion (~20-30%) of the putative formyl chloride intermediate may react with GSH and other cellular nucleophiles, instead of spontaneously decomposing to CO. According to these investigators, this portion of the oxidative pathway probably yields CO_2; a larger proportion of the formyl chloride intermediate decomposes to CO when cellular GSH is depleted. Metabolic pathways of bromochloromethane and other dihalomethanes are presented in Figure 5-1.

Gargas et al. (1986a) evaluated the kinetics of bromochloromethane metabolism, using 4-hour inhalation studies with male F344 rats. Gas uptake (disappearance) was determined during exposure to 200-4000 ppm (1058-21,168 mg/m^3) in a closed exposure chamber, and plasma bromide levels and carboxyhemoglobin levels were determined following exposure to constant concentrations of 51-2006 ppm (270-10,616 mg/m^3). The gas uptake data indicated that metabolism comprises both first-order and saturable components; similar data were found in other studies (see Section 5.1.). The oxidative pathway was high affinity and low capacity, with production of CO saturable at bromochlormethane concentrations greater than ~200 ppm; the maximum percent carboxyhemoglobin saturation attained was ~9%. The maximum



x = halogen atom

FIGURE 5-1

Proposed Pathways for Dihalomethane (CH_2X_2) Metabolism

Source: Gargas et al., 1986a

rate for the metabolism of bromochloromethane to CO was 54 µmol metabolized/kg/hour. The GSH pathway was low affinity but high capacity, and a single first-order process at all exposure concentrations.

Torkelson et al. (1960) determined inorganic bromide concentrations in the blood of four female rabbits (strain not specified) exposed to 130 ppm (688 mg/m³) bromochloromethane by inhalation for 7 hours/day, 5 days/week for 45 exposures in 66 days. Determinations were performed before and immediately after 1, 2, 5, 10, 14, 15 and 45 exposures. Maximum blood bromide ion concentrations (~30-35 mg/dℓ) were reached by the end of the second week.

Levels of inorganic bromide in the blood were determined in two female dogs (strain unspecified) after 3-4 and 13-14 weeks of 7 hours/day, 5 days/week inhalation exposure to a nominal bromochloromethane concentration of 1000 ppm (measured concentration ~890 ppm [4710 mg/m³]) (Svirbely et al., 1947). Blood bromide levels increased during daily exposure, did not significantly decline overnight or on days without exposure; however, the steady increase throughout the treatment period did not reach maximum by the end of treatment. Bromide ion levels in the blood were ~300-360 mg/dℓ at the end of treatment. These findings indicate a tendency for inorganic bromide to accumulate in the blood with continued exposure to bromochloromethane.

5.4. EXCRETION

Urinary output of inorganic bromide was determined in two female dogs (strain unspecified) after 3-4, 10 and 13-14 weeks of 7 hours/day, 5 days/week inhalation exposure to ~890 ppm (4710 mg/m³) bromochloromethane (Svirbely et al., 1947). Excretion of bromide markedly declined on exposure-free days, but tended to increase overall throughout the treatment

period. Information regarding the rate and extent of bromochloromethane excretion was not located in the available literature cited in Appendix A.

5.5. SUMMARY

Bromochloromethane is rapidly absorbed by rats in a biphasic manner following acute inhalation exposure (Gargas and Andersen, 1982), but quantitative data are not available regarding the extent of inhalation exposure or the rate or extent of oral exposure. There appears to be some distribution of bromide to the brain of dogs during subchronic inhalation exposure (Svirbely et al., 1947). Rat tissue:blood partition coefficients (Gargas et al., 1986a,b) suggest that bromochloromethane will distribute more readily to fat than to liver or muscle. Available data indicate that bromochloromethane is metabolized by two major pathways: an oxidative, cytochrome P-450 mediated pathway yielding CO and halide (putative formyl halide intermediate) and a glutathione (GSH)-dependent cytosolic pathway producing CO_2 and halide (Gargas et al., 1986a). It is proposed that a portion of the oxidative pathway also yields a significant amount of CO_2 (Gargas et al.,1986a). Information regarding the rate and extent of bromochloromethane excretion was not located in the literature cited in Appendix A.

6. EFFECTS

6.1. SYSTEMIC TOXICITY

6.1.1. ACUTE.

6.1.1.1. INHALATION EXPOSURE -- Rutstein (1963) reported that three male fire fighters who used chloro- bromomethane as a fire-extinguishing agent had gastrointestinal irritations (e.g., vomiting, stomach pains) and manifestations of CNS involvement (e.g., headache, loss of consciousness). Acute inhalation lethality data for bromochloromethane are summarized in Table 6-1. These data suggest that mice are more susceptible than rats since 7-hour exposures resulted in LC_{50}s of 2268-2995 ppm (12,000-15,850 mg/m³) for mice (Svirbely et al., 1947; Highman et al., 1948), and 7-hour exposures to 5000 ppm (26,460 mg/m³) were not lethal for rats (Torkelson et al., 1960). Death was often delayed in the mice but generally occurred during treatment in the rats exposed to 10,000 ppm. Signs observed in the mice and rats indicated CNS toxicity; these included restlessness, muscular twitching, uncoordinated movements, labored respiration and narcosis in the mice (Svirbely et al., 1947), and drowsiness and unconsciousness in the rats (Torkelson et al., 1960).

Highman et al. (1948) exposed Swiss mice (sex not reported) to 7-17 mg/ℓ (7000-17,000 mg/m³ or 1323-3212 ppm) bromochloromethane by inhalation 7 hours/day on 1-5 successive days. Histological examination of 79 mice immediately following exposure showed changes that included fatty degeneration of the liver after single exposures of $\geq$7 mg/ℓ and kidneys after single exposures of $\geq$12 mg/ℓ. These effects were most severe within 24 hours of exposure and were minimal or absent after 72 hours. Histological examinations were conducted on groups of four to five female rats (strain not reported) 24 hours following inhalation exposure to 600-40,000

ppm (113-7559 mg/m³) bromochloromethane for durations of 7-0.025 hours, respectively (Torkelson et al., 1960). Unequivocal alterations were observed only in the liver (small vacuoles in parenchyma not typical of fatty degeneration, often accompanied by increased liver weight). The minimum concentration producing hepatic effects after 7-hour exposure was 1500 ppm (7938 mg/m³); exposure to 600 ppm (5175 mg/m³) for 7 hours did not produce hepatic effects and exposure to 800 ppm (4234 mg/m³) for 7 hours produced equivocal hepatic histological alterations.

6.1.1.2. ORAL EXPOSURE -- Acute oral toxicity data are available for rats and mice. Torkelson et al. (1960) fed (apparently by gavage) an unspecified series of single doses of bromochloromethane in corn oil to groups of five male rats. Observation for 14 days showed that all rats survived a dose of 5 g/kg and all rats died within 24 hours after a dose of 7 g/kg. Additional information regarding this study was not reported. Groups of 10 mice (strain and sex not reported) were fed (method not reported) single doses of 500-4400 mg/kg bromochloromethane in olive oil (Svirbely et al., 1947). The LD_{50} (6-day observation) was ~4300 mg/kg. Signs showing dose-related CNS depression were observed at $\geq$500 mg/kg, but pathological examinations were not conducted and the lowest dose producing death was not reported. In a related study, unspecified numbers of Swiss mice (sex not reported) were administered single gavage doses of 0, 500, 3000 or 4500 mg/kg bromochloromethane in olive oil (Highman et al., 1948). Histological examinations conducted $\leq$96 hours after treatment showed no significant changes at 500 mg/kg.

Effects occurring at $\geq$3000 mg/kg included death, pronounced hepatic histopathology and other pathological changes similar to those resulting from acute inhalation exposure. Mice killed 24 hours after the initial

TABLE 6-1

Acute Inhalation Lethality of Bromochloromethane

Species	Strain/Sex	Concentration		Duration	Response	Reference
		mg/m³	ppm			
Mouse	Swiss/NR	2,995	15,850	7 hours	8-hour LC_{50}	Svirbely et al., 1947
Mouse	Swiss/NR	2,504	13,257	7 hours	24-hour LC_{05}	Svirbely et al., 1947
Mouse	Swiss/NR	2,436	12,891	7 hours	48-hour LC_{50}	Svirbely et al., 1947
Mouse	Swiss/NR	2,273	12,029	7 hours	72-hour LC_{50}	Svirbely et al., 1947
Mouse	Swiss/NR	2,551	13,500	1 week	18/20 died	Svirbely et al., 1947
Mouse	Swiss/NR	2,268	12,002	7 hours	72-hour LC_{50}	Highman et al., 1948
Rat	NR/M	5,000	26,460	7 hours	0/11 died	Torkelson et al., 1960
Rat	NR/F	5,000	26,460	7 hours	0/11 died	Torkelson et al., 1960
Rat	NR/M	10,000	52,920	4 hours	6/10 died	Torkelson et al., 1960
Rat	NR/F	10,000	52,920	4 hours	5/10 died	Torkelson et al., 1960

NR = Not reported

exposure had severe effects, which included focal subcapsular necrosis in the liver (12/50), hydropic degeneration in the liver (5/50) and hemoglobin casts in a few renal tubules (8/32). These effects were generally absent or slight in mice surviving ≥48 hours.

Highman et al. (1948) also treated a group of ~32 Swiss mice (sex not reported) with single gavage doses of 3000 mg/kg bromochloromethane in olive oil on 1-10 consecutive days. Several mice were sacrificed after each of the 10 doses. Histological examination of mice that died or were sacrificed showed fatty degeneration of the liver, kidney and sometimes heart. Other hepatic effects included subcapsular necrosis (23/32 mice), hydropic degeneration (8/32 mice) and an increased number of mononuclear periportal cells (8/32 mice). Effects were most severe 24-48 hours after the initial dose and became slight after 80 hours. Opacity of the eyes was observed in 5/19 mice surviving ≤3 days.

Occluded dermal application of bromochloromethane (5000 mg/kg) to clipped skin of five rabbits resulted in burns and denaturation of the skin with four surviving after 24 hours (Torkelson et al., 1960). Application without occlusion caused only slight defatting.

6.1.2. SUBCHRONIC.

6.1.2.1. **INHALATION EXPOSURE** -- Groups of 20 male and 20 female rats were exposed to nominal concentrations of 0, 500 or 1000 ppm bromochloromethane (490 ppm [2593 mg/m³] or 1010 ppm [5345 mg/m³] actual average concentrations) 7 hours/day for 79-82 exposures in 114 days (Torkelson et al., 1960). These concentration correspond to 0, 166.97-173.31 and 344.18-357.25 mg/kg/day assuming a body weight of 0.35 kg, a breathing rate of 0.223 m³/day and a 50% absorption of the inhaled dose. Because no effects were observed in male rats at 166.97-173.31 mg/kg/day, a group of 10

female rats were exposed to nominal concentrations of 0 or 400 ppm bromochloromethane (370 ppm [1958 mg/m³] actual average concentration) 7 hours/ day for 135 exposures in 195 days (4.85 days/week). This dose corresponds to 125.96 mg/kg/day assuming a body weight of 0.35 kg, a breathing rate of 0.223 m³/day and a 50% absorption of the inhaled dose. The strain of rats was not reported. Body weight gain and survival were evaluated throughout treatment and pathological examinations were conducted at termination. The pathological evaluation included gross examinations, organ weight determinations (lungs, heart, liver, kidney, spleen and testes) and histological examinations (organs that were weighed, pancreas and adrenals).

Hematological examinations of 10 females exposed to 0 or 344.18-357.25 mg/kg/day and blood bromide and blood nitrogen (urea nitrogen and nonprotein nitrogen) determinations of three rats/sex from each treatment and control group were also conducted at termination. Effects attributed to treatment included increased relative liver weights in females at 125.96 mg/kg/day and both sexes at $\geq$166.97-173.31 mg/kg/day, liver histopathology in females at 166.97-173.31 mg/kg/day (slight bile duct epithelial proliferation, slight portal fibrosis, occasional vacuolization) and both sexes at 344.18-357.25 mg/kg/day (effects similar to those at 166.97-173.31 mg/kg/day, cloudy swelling and vacuolization of hepatocytes) and increased relative kidney weights in both sexes at 344.18-357.25 mg/kg/day. Blood bromide levels were elevated in both sexes at all exposure concentrations, but effects typical of bromism (apathy, obesity, inactivity) were not observed. Terminal bromide ion levels were 44-73 mg/dℓ at 125.96 mg/kg/day and as high as 122 mg/dℓ at the higher concentrations.

Torkelson et al. (1960) also exposed 10 guinea pigs (strain not reported) of each sex to 0, 490 or 1010 ppm (2593 or 5345 mg/m³) bromochloromethane 7 hours/day, 5 days/week for 79-82 exposures in 114 days. These doses correspond to 0, 124.79-129.53 and 257.23-267.00 mg/kg/day assuming a body weight of 0.84 kg, a breathing rate of 0.4 m³/day and a 50% absorption of the inhaled dose. Evaluations of body weight, survival, pathology, blood bromide and blood nitrogen were conducted as in the rat study. Hematological examinations were conducted on three females from each group. Treatment-related effects included decreased body weights in both sexes at ≥124.79-129.53 mg/kg/day, increased relative liver weight in both sexes at ≥124.79-129.53 mg/kg/day, increased relative kidney weight in males at ≥124.79-129.53 mg/kg/day, an increased number of circulating neutrophils in females at ≥124.79-129.53 mg/kg/day and testicular effects at 344.18-357.25 mg/kg/day (Section 6.5.). Blood bromide levels were elevated in both sexes at both exposure levels.

Torkelson et al. (1960) also exposed 10 female mice (strain not reported) to 0, 490 or 1010 ppm (2593 or 5345 mg/m³) bromochloromethane 7 hours/day, 5 days/week for 79-82 exposures in 114 days. These dose correspond to 0, 340.67-353.59 and 702.22-728.88 mg/kg/day assuming a body weight of 0.03 kg, a breathing rate of 0.039 m³/day and a 50% absorption of the inhaled dose. Evaluations of body weight, survival and pathology were conducted as in the rat study. Blood bromide and blood nitrogen determinations and hematological examinations were not performed. Significantly decreased body weight and significanty increased relative liver and kidney weights occurred in both groups of treated mice.

Torkelson et al. (1960) also exposed two rabbits (strain not reported) of each sex to 0, 490 or 1010 ppm (2593 or 5345 mg/m³) bromochloromethane

7 hours/day, 5 days/week for 79-82 exposures in 114 days. These dose correspond to 0, 137.93-143.16 and 284.32-295.09 mg/kg/day assuming a body weight of 3.8 kg, a breathing rate of 2 m^3/day and a 50% absorption of the inhaled dose. Evaluations of body weight, survival and pathology were conducted as in the rat study. Blood bromide and blood nitrogen were determined in all treated and control rabbits except one treated female in the 137.93-143.16 mg/kg/day group. Hematological examinations were not performed. The histological examinations showed testicular alterations in one of the males exposed to 284.32-295.09 mg/kg/day (Section 6.5.). Blood bromide levels were elevated in both sexes at both exposure levels. Both sexes appeared to have elevated liver weights, but the small numbers of rabbits involved precluded definitive analysis. Results of the blood nitrogen determinations were not reported.

Torkelson et al. (1960) also exposed one male and one female dog (strain not reported) to 0 or 370 ppm (1958 mg/m^3) bromochloromethane 7 hours/day, 5 days/week for 135 exposures in 195 days. These doses correspond to 0 and 66.93 mg/kg/day assuming a body weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. Evaluations of body weight, survival, blood bromide, blood nitrogen and hematology were conducted as in the rat study. Pathological examinations were not performed. The only effect reported was elevated blood bromide levels.

Groups of 50 male and 50 female albino rats (descendants of germ-free Wistar rats) were exposed to nominal concentrations of 500 or 1000 ppm bromochloromethane 6 hours/day, 5 days/week for 6 months for a total of 124 exposures (MacEwen et al., 1966). Actual measured concentrations averaged 515 and 1010 ppm (2725 and 5345 mg/m^3), respectively. These doses correspond to 0, 149.51 and 293.26 mg/kg/day assuming an average body weight

of 0.35 kg, a breathing rate of 0.223 m^3/day and a 50% absorption of the inhaled dose. Fifty chamber air-exposed male rats served as controls. Body weight, serum bromide levels and survival were evaluated throughout the treatment period. After 2 and 4 months of exposure, groups of 10 rats in each treatment group and five control rats were subjected to white blood cell count and clinical chemistry determinations and sacrificed for organ weight and histological examinations. The remainder of the rats were evaluated at the termination of treatment. The clinical tests consisted of SGOT, SGPT, total protein, albumin and A/G ratio. It is not specified whether organs other than liver, kidney and spleen were weighed and histologically examined. The only effect attributable to treatment was a significantly ($p \leq 0.01$) dose-related decreased body weight gain in male rats at $\geq$149.51 mg/kg/day, the magnitude of which increased with increasing duration of exposure. Blood bromide levels were increased at both concentrations throughout the treatment period. The investigators indicated that similar levels of blood bromide in humans may produce mild sedation and suggested that lethargy and altered eating habits may have been responsible for the reduction in body weight gain.

MacEwen et al. (1966) also exposed four male and four female beagle dogs to 0, 515 or 1010 ppm (2725 or 5345 mg/m^3) bromochloromethane 6 hours/day, 5 days/week for 6 months for a total of 124 exposures. These doses correspond to 0, 79.45 and 155.84 mg/kg/day assuming an average body weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. Toxicity was evaluated as in the rat study with the addition of other clinical chemistry tests. Evaluations were performed on groups of two treated and one control dog after 2 and 4 months and on the remaining

animals at termination of treatment. The only effect attributed to treatment was increased serum bromide levels at both concentrations throughout the treatment period.

Twenty male rats (strain not reported) were exposed to 1000 ppm bromochloromethane (nominal concentration) 7 hours/day, 5 days/week for 14 weeks (Svirbely et al., 1947). The measured concentration was generally 11% lower than the calculated value (i.e., 890 ppm or 4710 mg/m^3). This dose corresponds to 299.20 mg/kg/day assuming an average body weight of 0.35 kg, a breathing rate of 0.223 m^3/day and a 50% absorption of the inhaled dose. A control group appears to have been used, but specific information was not reported. Weight gain and survival throughout treatment, histology after 67 exposures (19 rats) and bromide levels in the blood and brain immediately after the last exposure were evaluated. It is not indicated whether tissues other than liver and spleen were histologically examined. Effects consisted of a slight increase of hemosiderin in the spleen and increased concentrations of bromide in the blood and brain.

Svirbely et al. (1947) also exposed three male rabbits and two female dogs (strains not reported) to 1000 ppm bromochloromethane (measured concentration ~890 ppm [4710 mg/m^3]) 7 hours/day, 5 days/week for 14 weeks. In rabbits this dose corresponds to 247.16 mg/kg/day assuming an average body weight of 3.8 kg, a breathing rate of 2 m^3/day and a 50% absorption of the inhaled dose. In dogs this dose corresponds to 158.99 mg/kg/day assuming an average body weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. Toxicity was evaluated as in the rat study with the addition of hematological examinations in both species at "regular" intervals, liver function evaluation (bromsulfalein excretion) and urinalysis in dogs at "regular" intervals and blood inorganic bromide determinations in dogs throughout the treatment period. Effects consisting of a

slight increase of hemosiderin in the spleen and kidneys and an increase in fat in the kidneys occurred in the dogs. Inorganic bromide accumulated in the blood of the dogs throughout treatment (terminal concentrations were ~300-360 mg/dℓ).

Highman et al. (1948) exposed 100 Strain A mice (sex not reported, age 2 months) and 45 C3H mice (sex not reported, age 3-7 months) to 1000 ppm (5292 mg/m³) bromochloromethane. Use of control groups was not indicated. Exposures were administered 5 times/week with occasional long rest periods of unspecified frequency and duration when necessary, as indicated by mortality and abnormal general condition. Calculation of a dose in mg/kg/day is uncertain given these experimental conditions. Surviving Strain A mice each received a total of 64 exposures of 3-7 hours in a period of ~5 months (approximately 143.97-335.93 mg/kg/day corresponding to 3 or 7 hour dosing schedule and assuming an average body weight of 0.03 kg, a breathing rate of 0.039 m³/day and a 50% absorption of the inhaled dose; surviving C3H mice each received a total of 49 exposures of 3-7 hours in a period of 4 months (approximately 150.43-351 mg/kg/day corresponding to 3 or 7 hour dosing schedule and assuming an average body weight of 0.03 kg, a breathing rate of 0.039 m³/day and a 50% absorption of the ihhaled dose). Most of the mice died at unspecified, irregular intervals during treatment, and some died or were sacrificed at unspecified intervals following treatment. A total of 21 mice (one Strain A and 20 C_3H) survived until terminal sacrifice at 13-16 months of age. Histological examinations were conducted on mice that were sacrificed and some (number unspecified) that died. The mice that died during exposure generally showed slight fatty changes in the liver and kidneys. Extensive tubular necrosis of the inner zone of the renal cortex was observed in two strain A mice that died during

the fourth daily exposure. Several other mice that died during exposure showed coagulation or karyorrhectic necrosis of a few isolated liver cells. Treatment-related effects were not observed in the mice that survived until terminal sacrifice.

6.1.2.2. **ORAL EXPOSURE** -- Pertinent data regarding subchronic oral exposure of humans or animals to bromochloromethane were not located in the available literature cited in Appendix A.

6.1.3. Chronic

6.1.3.1. **INHALATION EXPOSURE** -- Pertinent data regarding the chronic inhalation exposure of humans or animals to bromochloromethane were not located in the available literature cited in Appendix A.

6.1.3.2. Oral Exposure -- Pertinent data regarding the subchronic or chronic oral exposure of humans or animals to bromochloromethane were not located in the available literature cited in Appendix A.

6.2. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of bromochloromethane to humans or animals following exposure by inhalation, oral or other routes of exposure were not located in the available literature cited in Appendix A.

6.3. GENOTOXICITY

Data from genotoxicity tests with bromochloromethane are presented in Table 6-2. Consistently positive results were observed in the reverse mutation test in Salmonella typhimurium (Simmon et al., 1977; Strobel and Grummt, 1987; Osterman-Golkar et al., 1983). Metabolic activation was not required but increased the response in TA98 and TA100 (Strobel and Grummt, 1987). Positive results were also observed in the reverse mutation and lambda prophage induction tests in Escherichia coli (Osterman-Golkar et al., 1983). Negative results were observed in the mitotic recombination test in

TABLE 6-2

Genotoxicity Testing of Bromochloromethane*

Assay	Indicator Organism	Application	Purity (%)	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535, TA1537, TA1538, TA98, TA100	vapor in dessicators	NR	10, 20 or 50 µL in dessicators	-	+	Dose-related response in TA100; response in other strains and with Aroclor-induced rat liver activation not reported	Simmon et al., 1977
Reverse mutation	S. typhimurium TA97, TA98, TA100, TA104	plate incorporation	NR	10-1000 µg/plate	±S9	+ +	Positive in all four strains, S9 enhanced the response in TA98, TA100	Strobel and Grummt, 1987
Reverse mutation	S. typhimurium TA1535, TA100	spot test	NR	10 µL/disk	NR	+	Stronger response in TA1535; incubated in dessicators	Osterman-Golkar et al., 1983
Reverse mutation	S. typhimurium TA100	preincubation	NR	~20-60 mM	NR	+	Dose-related response between 20-40 mM	Osterman-Golkar et al., 1983
Reverse mutation	Escherichia coli Sd-4, WU361089	spot test	NR	10 µL/disk	NR	+	Strongly positive in WU361089, equivalent in Sd-4	Osterman-Golkar et al, 1983
Labda prophage induction	E. coli K39	spot test	NR	10 µL/disk	NR	+	NC	Osterman-Golkar et al., 1983
Mitotic recombination	Saccharomyces cerevisiae D3	liquid suspension	NR	0.1 of 0.2%	±S9	=	NC	Simmon, 1976
SCE, chromosomal aberrations	Chinese hamster FAF cells	cell culture	NR	$1X10^{-4}$ to $5X10^{-3}$ M	-	+	Dose-related response in SCE and chromosomal aberrations; cytotoxic at highest concentration	Strobel and Grummt, 1987

*The purity of the compound was not reported.

NC = No comment; NR = not reported

Saccharomyces cerevisiae (Simmon, 1976). In the only mammalian test located, bromochloromethane induced SCEs and chromosomal aberrations in Chinese hamster FAF cells (Strobel and Grummt, 1987).

6.4. DEVELOPMENTAL TOXICITY

Pertinent data regarding the developmental toxicity of bromochloromethane were not located in the available literature cited in Appendix A.

6.5. OTHER REPRODUCTIVE EFFECTS

Torkelson et al. (1960) exposed groups of 10 male guinea pigs (strain not reported) to 0, 490 or 1010 ppm bromochloromethane 7 hours/day, 5 days/week for 79-82 exposures in 114 days (see Section 6.1.1.1.). These dose correspond to 0, 124.79-129.53 and 257.23-267.00 mg/kg/day assuming an average body weight of 0.84 kg, a breathing rate of 0.4 m^3/day and a 50% absorption of the inhaled dose. Histological examination of the testes showed decreased spermatogenesis in the tubules and fibrosis in numerous tubules with only germinal epithelium remaining in the other tubules at 257.23-267.00 mg/kg/day. The average testes-to-body weight ratio was decreased at 257.23-267.00 mg/kg/day (0.38 vs. 0.46 at 0 and 124.79-129.53 mg/kg/day), but statistical significance was not reported. Reproductive function was not evaluated.

Torkelson et al. (1960) also exposed groups of two male rabbits (strain not reported) to 0, 490 or 1010 ppm (2593 or 5345 mg/m^3) bromochloromethane 7 hours/day, 5 days/week for 79-82 exposures in 114 days (see Section 6.1.1.1.). These doses correspond to 0, 137.93-143.16 and 284.32-295.09 mg/kg/day assuming an average body weight of 3.8 kg, a breathing rate of 2 m^3/day and a 50% absorption of the inhaled dose. Histological examination showed testicular tubule changes, characterized by decreased spermatogenesis with replacement fibrosis in one of the rabbits

exposed to 284.32-295.09 mg/kg/day. The testicular histology of the other rabbit was normal. The average testes-to-body weight ratio for the rats in the 284.32-295.09 mg/kg/day group (0.08) was lower than the ratios for the 0 and 137.93-143.16 mg/kg/day groups (0.16 and 0.17, respectively). Reproductive function was not evaluated.

6.6. SUMMARY

Inhalation LC_{50}s for mice for 7-hour exposures ranged from 2268-2995 ppm (Svirbely et al., 1947; Highman et al., 1948) and exposure to 5000 ppm (26,460 mg/m³) for 7 hours was not lethal for rats (Torkelson et al., 1960). Rats survived a single oral dose of 5 g/kg, and all rats died within 24 hours after a dose of 7 g/kg (Torkelson et al., 1960). An oral LD_{50} of ~4300 mg/kg was determined for mice (Svirbely et al., 1947). Signs and pathological effects of acute inhalation and oral exposure to bromochloromethane are similar; principal effects include CNS depression and degeneration of the liver.

Subchronic inhalation studies of bromochloromethane have been conducted with rats, mice, guinea pigs, rabbits and dogs (Torkelson et al., 1960; MacEwen et al., 1966; Svirbely et al., 1947; Highman et al., 1948). Concentrations ranged from 66.93 mg/kg/day (dogs) to 728.88 mg/kg/day (mice); exposures were usually 5-7 hours/day, 5 days/week ranging from 14 weeks to ~6 months. Generally, minor effects such as decreased body weight, increased relative liver and kidney weight and reversible liver and kidney histological alterations occurred at concentrations $\geq$500 ppm in most species evaluated for these endpoints. Torkelson et al. (1960) found that relative liver weight was increased in rats at concentrations of 125.96 mg/kg/day. With histological effects occurring at 166.97-173.31 mg/kg/day, exposure to 1000 ppm (143.97-335.93 mg/kg/day) caused death and marked liver injury in

mice (Highman et al., 1948); however, exposure conditions were not reported adequately and calculation of this dose to mg/kg/day can not be done accurately without further information. Information regarding the chronic inhalation toxicity, subchronic or chronic oral toxicity or teratogenicity of bromochloromethane were not located. Decreased spermatogenesis and fibrosis occurred in the tubules of the testes of guinea pigs and rabbits that were subchronically exposed to 344.18-357.25 and 257.23-267.00 mg/kg/day respectively, to bromochloromethane by inhalation (Torkelson et al., 1960). The functional significance of these effects was not evaluated.

The carcinogenicity of bromochloromethane has not been evaluated. Bromochloromethane was mutagenic in Salmonella typhimurium and Escherichia coli bacteria (Simmon et al., 1977; Osterman-Golkar et al., 1983; Strobel and Grummt, 1987) and induced SCE and chromosome aberrations in Chinese hamster cells in vitro (Strobel and Grummt, 1987).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1989) recommends a TLV-TWA of 200 ppm (1058 mg/m³) and a TLV-STEL of 250 ppm (1320 mg/m³) for occupational exposure to bromochloromethane, but deletion of the STEL is proposed. The recommendation for the TLV-TWA is based primarily on the subchronic animal studies evaluated in Section 6.1.1.1. (ACGIH, 1986). OSHA (1989) has promulgated a PEL of 200 ppm (~1050 mg/m³) for occupational exposure to bromochloromethane.

Based on inhalation toxicity data, U.S. EPA (1988) has derived 1-day, 10-day, longer-term (child) and longer-term (adult) drinking water HAs of 50 mg/ℓ, 50 mg/ℓ, 13.1 mg/ℓ and 45.7 mg/ℓ, respectively, for bromochloromethane. U.S. EPA (1988) also calculated a provisional DWEL of 4.6 mg/ℓ for bromochloromethane.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic life from exposure to bromochloromethane were not located in the available literature cited in Appendix A.

8. RISK ASSESSMENT

8.1. CARCINOGENICITY

8.1.1. Inhalation. Pertinent data regarding the carcinogenicity of bromochloromethane to humans or animals by inhalation exposure were not located in the available literature cited in Appendix A. Bromochloromethane has not been scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1989).

8.1.2. Oral. Pertinent data regarding the carcinogenicity of bromochloromethane to humans or animals by oral exposure were not located in the available literature cited in Appendix A.

8.1.3. Other Routes. Pertinent data regarding the carcinogenicity of bromochloromethane to humans or animals by other routes of exposure were not located in the available literature cited in Appendix A.

8.1.4. Weight of Evidence. Pertinent carcinogenicity data for humans and animals were not located in the available literature cited in Appendix A; therefore, bromochloromethane is categorized in U.S. EPA weight-of-evidence Group D (Not Classifiable as to Human Carcinogenicity) using the U.S. EPA (1986c) classification scheme.

8.1.5. Quantitative Risk Estimates. Derivation of a carcinogenic potency factor for bromochloromethane is precluded by the lack of appropriate data.

8.2. SYSTEMIC TOXICITY

8.2.1. Acute Exposure.

8.2.1.1. INHALATION -- Acute inhalation lethality data for bromochloromethane are summarized in Table 6-1. These data suggest that mice are more susceptible to bromochloromethane exposure by inhalation than are rats. Hallmarks of CNS toxicity in mice and rats includes restlessness,

muscular twitching, uncoordinatedmovements, labored respiration, narcosis (mice), drowsiness (rats) and unconsciousness (rats). Highman et al. (1948) demonstrated fatty degeneration of the liver in Swiss mice after a single expousre ≥7 mg/ℓ bromochloromethane and degeneration of the kidneys after a single exposure to ≥12 mg/ℓ bromochloromethane. Torkelson et al. (1960) demonstrated that liver and kidney degeneration in rats occured after a single 7 hour expousure to 1500 ppm, equivocal results at 800 ppm, no degeneration at 600 ppm bromochloromethane.

8.2.1.2. **ORAL** -- Torkelson et al. (1960) determines that a 7 g/kg dose of bromochloromethane was lethal to all rats within 24 hours of dosing but that all rats survived a dose of 5 g/kg. Svirbely et al. (1947) determined a 6-day LD_{50} to be 4300 mg/kg in mice. Signs of CNS depression were observed at doses ≥ 500 mg/kg. Highman et al. (1948) demonstrated effects in mice at ≥ 3000 mg/kg including pronouned hepatic histopathology and other acute pathological changes. Mice killed 24 hours after dosing had severe effects including focal subcapsular necrosis and hydropic degeneration of the liver and hemoglobin casts in a few renal tubules. These effects were generally absent or slight in mice surviving ≥48 hours.

Occluded dermal application of 5000 mg/kg bromochloromethane to the clipped skin of five rabbits resulted in burns and denaturation of the skin. Application without occlusion only caused slight defatting.

8.2.2. Subchronic Exposure.

8.2.2.1. **INHALATION** -- Sufficient data are available for derivation of a subchronic inhalation RfD for bromochloromethane. Inhalation RfD derivation involves evaluating the quality of the inhalation exposure-response data, converting exposure concentrations associated with effects in

animals to human equivalent concentrations and dividing these by uncertainty factors and modifying factors. For gases such as bromochloromethane, which produce systemic effects and reach steady state within the daily exposure length, HECs are calculated by adjusting the animal exposure concentrations to equivalent continuous exposure concentrations and multiplying by the ratio of the blood/gas partition coefficient in the experimental animal to that in humans.

Evidence for rapid attainment of steady state with bromochloromethane is provided by Gargas and Andersen (1982), who found that the rapid uptake phase in rats was completed in 70-110 minutes (see Section 5.1.). A blood/gas partition coefficient for bromochloromethane of 41.5 was reported for rats (see Section 5.2.), but not for humans. Insufficient data for a blood/gas partition coefficient for bromochloromethane was found for humans; therefore, the ratio of the animal to human blood/gas partition coefficients is assumed to be 1. Therefore, HECs (Human equivalent concentrations) for extrarespiratory effects from bromochloromethane are identical to the adjusted animal exposure concentration.

Torkelson et al. (1960) exposed 10 female rats (strain not reported) to 370 ppm (1958 mg/m^3) bromochloromethane 7 hours/day for 135 exposures in 195 days, and groups of 20 rats/sex (strain not reported) to 490 ppm (2593 mg/m^3) or 1010 ppm (5345 mg/m^3) bromochloromethane 7 hours/day for 79-82 exposures in 114 days. These doses correspond to 125.96 mg/kg/day (370 ppm); 166.97-173.31 mg/kg/day (490 ppm); and 344.18-357.25 mg/kg/day (1010 ppm) assuming an average body weight of 0.35 kg, a breathing rate of 0.233 m^3/day and a 50% absorption of th inhaled dose. Effects attributed to treatment included increased liver-to-body weight ratios at $\geq$125.96 mg/kg/day, liver histological alterations (e.g., slight fibrosis and

vacuolization) in females at 166.97-173.31 mg/kg/day and both sexes at 344.18-357.25 mg/kg/day and increased kidney-to-body weight ratio in both sexes at 344.18-357.25 mg/kg/day. Abnormal hematology, increased blood nitrogen levels, decreased body weight gain or symptoms of bromism were not observed at any of the exposure concentrations. As the increased relative liver weight was not accompanied by histological alterations or other effects at 125.96 mg/kg/day, this concentration represents a NOAEL and 166.97-173.31 mg/kg/day is the lowest LOAEL (Recs. #1 and 2, Appendix C). Dogs (1/sex) were also exposed to 370 ppm (1958 mg/m^3) bromochloromethane 7 hours/day for 135 exposures in 195 days. This exposure corresponds to 66.93 mg/kg/day assuming an average bodw weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. There were no effects on body weight, blood nitrogen or hematology, but histological examinations and organ weight measurements were not performed. Although 66.93 mg/kg/day is a NOEL in dogs (Rec. #7, Appendix C), this value is not suitable for quantitative risk assess- ment because of the small number of animals and lack of histology.

Albino rats (50/sex/concentration) and beagle dogs (4/sex/concentration) were exposed to 515 or 1010 ppm (2725 or 5345 mg/m^3) bromochloromethane 6 hours/day for 124 exposures in 6 months (MacEwen et al., 1966). In rats these doses corresponds to 149.51 and 293.26 mg/kg/day assuming an average body weight of 0.35 kg, a breathing rate of 0.223 m^3/day and a 50% absorption of the inhaled dose. In beagle dogs these doses correspond to 79.45 and 155.84 mg/kg/day respectively, assuming an average body weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. Decreased body weight gain in male rats at $\geq$149.51 mg/kg/day, possibly from lethargy associated with elevated blood bromide concentration, was the only effect attributed to treatment. Histological examinations of

the liver and other tissues, organ weight measurements and clinical chemistry evaluations (including SGOT and SGPT) were unremarkable. In this study, 149.51 mg/kg/day is considered a LOAEL associated with reduced growth rate in rats possibly from bromide-induced lethargy (Rec. #8, Appendix C).

Twenty male rats (Rec. #10, Appendix C), two female dogs (Rec. #12, Appendix C) and three male rabbits (Rec. #11, Appendix C) (strains not reported) were exposed to 890 ppm (4710 mg/m^3) bromochloromethane (nominal concentration) 7 hours/day, 5 days/week for 67 exposures (~14 weeks) (Svirbely et al., 1947). In rats this dose corresponds to 299.20 mg/kg/day assuming an average body weight of 0.35 kg, a breathing rate of 0.223 m^3/day and a 50% absorption of the inhaled dose. In dogs this dose corresponds to 158.99 mg/kg/day assuming an average body weight of 12.7 kg, a breathing rate of 4.3 m^3/day and a 50% absorption of the inhaled dose. In rabbits this dose corresponds to 247.16 mg/kg/day assuming an average bodw weight of 3.8 kg, a breathing rate of 2.0 m^3/day and a 50% absorption of the inhaled dose. Slightly increased hemosiderin occurred in the rats (spleen) and dogs (spleen and kidneys), and increased fat occurred in the kidneys of dogs. Other histological alterations such as liver were not observed and body weight measurements (all species), liver function evaluation (dogs, rabbits) and urinalysis (dogs, rabbits) were unremarkable. The 247.16 mg/kg/day concentration, therefore, is a NOEL in rabbits and the 299.20 mg/kg/day is a LOAEL in rats and 158.99 mg/kg/day is a LOAEL in dogs.

Guinea pigs (10/sex/concentration) (Rec. #3, Appendix C), mice (10/sex/concentration) (Rec. #4, Appendix C) and rabbits (2/sex/concentration) (Rec. #5, Appendix C) were exposed to 0, 490 or 1010 ppm (2593 or 5345 mg/m^3) bromochlormethane 7 hours/day for 79-82 exposures in 114 days (Torkelson et al., 1960). In guinea pigs these doses correspond to 0. 124.79-129.53 and 257.23-267.00 mg/kg/day respectively, assuming an average body weight of

0.84 kg, a breathing rae of 0.4 m^3/day and a 50% absorption of the inhaled dose. In mice these doses corresponds to 0, 340.67-353.59 and 702.22-728.88 mg/kg/day respectively, assuming an average body weight 0.03 kg, a breathing rate of 0.039 m^3/day and a 50% absorption of the inhaled dose. In rabbits these dogs corresponds to 0, 137.93-143.16 and 284.32-295.09 mg/kg/day respectively, assuming an average body weight of 3.8 kg, a breathing rate of 2 m^3/day and a 50% absorption of the inhaled dose. The 124.79-129.53 mg/kg/day concentration is a LOAEL in the guinea pigs and the 340.67-353.59 mg/kg/day concentration is a LOAEL in mice, associated with decreased body weight, increased relative liver and kidney weights and neutrophilia (female guinea pigs). Adverse effects in rabbits were limited to testicular lesions at the 284.32-295.09 mg/kg/day level

One hundred Strain A mice and 45 C3H mice (sexes not reported) were exposed for 3-7 hours/day to 1000 ppm (5292 mg/m^3) bromochloromethane for $\leq$64 exposures in 5 months ($\leq$143.97-335.93 mg/kg/day assuming an average body weight of 0.03 kg, a breathing rate of 0.039 m^3/day and a 50% absorption of the inhaled dose) and 49 exposures in 4 months (150.43-351.00 mg/kg/day assuming an average body weight of 0.03 kg, a breathing rate of 0.039 m^3/day and a 50% absorption of the inhaled dose), respectively (Highman et al., 1948). The exposures were administered 5 days/week but were interrupted by occasional long rest periods (duration and frequency not reported) when necessary, as indicated by mortality or abnormal general condition. Most of the mice (numbers not reported) died during the exposure period and the mice that died generally had slight fatty changes in the liver and kidneys. The exposure schedule was not reported in sufficient detail to permit consideration of this study for quantitative risk assessment.

Acute toxicity data indicate that the critical effects of exposure to bromochloromethane appear to be CNS involvement and hepatotoxicity (Rutstein, 1963; Svirbely et al., 1947; Torkelson et al., 1960). In the subchronic inhalation studies, reduced rate of body weight gain and elevated liver weight were the first effects reported at the lower concentrations. In the absence of histopathological alteration or biochemical evidence of organ damage or impaired function, elevated liver weight alone may be considered a nonadverse effect. Similarly, a slight reduction in growth with no evidence of organic injury or compromised function may be considered nonadverse. Several studies, however, have shown that bromide ion is a consistent metabolite of bromochloromethane in the mammalian species studied, and that blood levels of bromide increase in a dose-related manner in animals exposed by inhalation (Svirbely et al., 1947; Torkelson et al., 1960; MacEwen et al., 1966; Gargas et al., 1986a). MacEwen et al. (1966) postulated that the reduced body weight gain observed in rats exposed to bromochloromethane may have resulted from lethargy induced by elevated blood bromide levels. The conservative approach, therefore, is to consider reduced body weight gain a potentially adverse effect of inhalation exposure to bromochloromethane.

Reduced body weight gain was reported in all species studied (except rabbits) in the subchronic inhalation studies reviewed herein. The NOAEL for this effect in rats was the 125.96 mg/kg/daylevel in the 195-day study (Rec. #1, Appendix C) by Torkelson et al. (1960). Using this NOAEL and an uncertainty factor of 1000 (10 to reflect uncertainties associated with estimating a human equivalent concentration from animal exposure data, 10 to reflect uncertinties associated with extrapolation from a subchronic study of chronic toxicity endpoints, and 10 to protect the most sensitive

individuals) a chronic RfD of 1.26E-02 mg/kg/day is calculated. Confidence in the key study is low because of the relatively small number of animals and lack of treated males at the lowest (NOAEL) concentration. Confidence in the data base and RfD are low because of the lack of developmental and reproductive data and the lack of adequate evaluation of the effect of bromochloromethane (elevated blood bromide levels) on CNS function, which could be the critical effect of exposure.

Two previous risk assessments of bromochloromethane have been performed by the U.S. EPA. An RfD was not calculated in a Health and Environmental Effects Profile (U.S. EPA, 1985) because the Torkelson et al. (1960) rat study was considered inadequate. It did not clearly define a NOAEL for liver effects and did not test males at the NOAEL concentration. The same NOAEL, however, was considered sufficient basis for deriving drinking water longer-term HAs and a provisional DWEL for bromochloromethane (U.S. EPA, 1988).

8.2.2.2. ORAL -- Information on the subchronic oral toxicity of bromochloromethane was not located. Acute exposure data, however, indicate that the critical effects of both inhalation and oral exposure are CNS signs and hepatotoxicity. In addition, the critical effects of subchronic inhalation exposure to bromochloromethane are reduced body weight and hepatotoxicity. The respiratory tract does not appear to be the target organ for inhalation exposure to bromochloromethane. The data reviewed in Section 5.3. suggest that metabolism involving dehalogenation would be expected with either route of exposure. Therefore, in the absence of subchronic oral data, it is appropriate to use inhalation toxicity data to derive a subchronic oral RfD for bromochloromethane.

As discussed in Section 8.2.2.1., a NOAEL of 125.96 mg/kg/day has been identified in rats exposed to bromochloromethane for 7 hours/day 135 exposures in 195 days (Torkelson et al., 1960) (Rec. #1, Appendix C). This dose is essentially the same as a previously derived estimated absorbed dose of 130.5 mg/kg/day based on the same NOAEL used to calculate longer-term drinking water HAs (U.S. EPA, 1988). Applying an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to protect most sensitive individuals), the subchronic oral RfD for bromo- chloromethane is 1 mg/kg/day. Confidence in the key study is low (see Section 8.2.1.1.). Low confidence in the data base and RfD are due to the lack of oral toxicity data.

8.2.3. Chronic Exposure.

8.2.3.1. INHALATION -- Chronic inhalation studies of bromo-chloromethane have not been conducted. It is appropriate, therefore, to derive a chronic inhalation RfD for bromochloromethane based on subchronic data. Using the subchronic inhalation RfD of 1.26E-1 (see Section 8.2.1.1.) and an additional uncertainty factor of 10 to extrapolate from subchronic to chronic exposure, the chronic inhalation RfD is 1.26E-2. Confidence in the RfD is low because of the lack of chronic data, and because confidence in the subchronic inhalation RfD is low.

8.2.3.2. ORAL -- Data on the chronic oral toxicity of bromochloromethane were not located. It is appropriate to derive a chronic oral RfD for bromochloromethane based on the subchronic oral RfD because of lack of chronic data. Using the subchronic oral RfD of 1 mg/kg/day (see Section 8.2.2.1.) and an additional uncertainty factor of 10 to extrapolate from subchronic to chronic exposure, the chronic oral RfD is 0.1 mg/kg/day.

This RfD is the same as a previously derived RfD of 0.13 mg/kg/day used to calculate a provisional DWEL for lifetime exposure (U.S. EPA, 1988). Confidence in the key study is low (see Section 8.2.1.1.), and confidence in the data base and RfD are low because of the lack of oral toxicity data.

9. REPORTABLE QUANTITIES

9.1. BASED ON SYSTEMIC TOXICITY

The toxicity of bromochloromethane is discussed in Chapter 6, and inhalation data suitable for RQ derivation are summarized in Table 9-1. Chronic inhalation data and oral data useful for RQ derivation are not available.

As shown in Table 9-1, subchronic inhalation exposure to bromochloromethane produced decreased body weight gain in rats, mice and guinea pigs (MacEwen et al., 1966; Torkelson et al., 1960), increased relative organ weights (liver and/or kidneys) in rats, mice and guinea pigs (Torkelson et al., 1960), histological alterations in the liver in rats (Torkelson et al., 1960) and kidneys in dogs (Svirbely et al., 1947), increased hemosiderin in the spleen of rats (Svirbely et al., 1947) and testicular effects in guinea pigs and rabbits (Torkelson et al., 1960). Death in mice (Highman et al., 1948) was not included because the exposure protocol was not presented in sufficient detail from which to estimate a transformed animal dose.

Derivations of CSs for bromochloromethane, based on the lowest equivalent human dose associated with each effect in Table 9-1, are presented in Table 9-2. Changes in body and organ weights are assigned an RV_e of 4. The most appropriate RV_e for the kidney histological alterations is 5 because the effects were slight and reversible. Lesions in the liver included fibrosis, which may not be reversible; liver lesions were assigned an RV_e of 6. Increased hemosiderin warrants an RV_e of 1 since hematin formation is most appropriately viewed as a biochemical effect. The most appropriate RV_e for the testicular alterations is 6 because it cannot be determined if the effects were sufficient to impair fuction. Five of the six CSs correspond to an RQ of 1000. The highest CS (12.22) for liver lesions in rats (Torkelson et al., 1960) is used as the basis for the RQ

TABLE 9-1

Inhalation Toxicity Summary for Bromochloromethane

Species/ Strain	Sex	No. at Start	Average Weight[a] (kg)	Purity (%)	Exposure	Transformed Animal Dose[b] (mg/kg/day)	Equivalent Human Dose[c] (mg/kg/day)	Response	Reference
Rat/NR	F	10	0.35	>99%	370 ppm (1958 mg/m³), 7 hours/day for 135 exposures in 195 days	125.96	2.15	Increased relative liver weight	Torkelson et al., 1960
Rat/NR	F	20	0.35	>99%	490 ppm (2593 mg/m³), 7 hours/day for 79-82 exposures in 114 days	166.97-173.31[d]	2.86-2.96[d]	Histological alterations in the liver	Torkelson et al., 1960
Rat/Wistar	M	50	0.32[e]	98.8%	515 ppm (2725 mg/m³), 6 hours/day, for 124 exposures in 6 months	163.55	2.71	Decreased body weight gain	MacEwen et al., 1966
Rat/NR	M	20	0.35	high	890 ppm (4710 mg/m³), 7 hours/day 5 days/week for 67 exposures (~14 weeks)	312.59	5.35	Increased hemosiderin in spleen	Svirbely et al., 1947
Mouse/NR	F	10	0.03	>99%	490 ppm (2593 mg/m³), 7 hours/day for 79-82 exposures in 114 days	340.68-353.61[d]	2.57-2.67[d]	Increased relative liver weight, decreased body weight	Torkelson et al., 1960
Rabbit/NR	M	2	3.8	>99%	1010 ppm (5345 mg/m³), 7 hours/day for 79-82 exposures in 114 days	284.29-295.09[d]	10.76-11.17[d]	Testicular effects	Torkelson et al., 1960
Dog/NR	F	2	12.7	high	890 ppm (4710 mg/m³), 7 hours/day, 5 days/week for 67 exposures (~14 weeks)	166.11	9.40	Histological alterations in the kidneys	Svirbely et al., 1947
Guinea pig/ NR	M,F	10/sex	0.84	>99%	490 ppm (2593 mg/m³), 7 hours/day for 79-82 exposures in 114 days	124.79-129.53[d]	2.86-2.97[d]	Increased relative liver and kidney weights, decreased body weights	Torkelson et al., 1960

TABLE 9-1 (cont.)

Species/ Strain	Sex	No. at Start	Average Weight[a] (kg)	Purity (%)	Exposure	Transformed Animal Dose[b] (mg/kg/day)	Equivalent Human Dose[c] (mg/kg/day)	Response	Reference
Guinea pig/ NR	M	10	0.84	>99%	1010 ppm (5345 mg/m³), 7 hours/day for 79-82 exposures in 114 days	257.22-266.99[d]	5.89-6.11[d]	Testicular effects	Torkelson et al., 1960

[a]Reference body weight for rats (U.S. EPA, 1980), mice (U.S. EPA, 1980) and other species (U.S. EPA, 1986c,d) unless indicated otherwise.

[b]Transformed doses were calculated by adjusting the exposure concentration in mg/m³ to equivalent continous exposure concentrations, multiplying by the animal inhalation rate and dividing by the animal body weight. Reference inhalation rates of 0.223 m³/day for rats (U.S. EPA, 1980), 0.039 m³/day for mice (U.S. EPA, 1980), 0.40 m³/day for guinea pigs (U.S. EPA, 1986d), 2.0 m³/day for rabbits (U.S. EPA, 1986d) and 4.3 m³/day for dogs (U.S. EPA, 1986d) were used except for the MacEwen et al. (1966) rat study. An inhalation rate of 9.269 m³/day was estimated for rats in this study using an allo-metric equation (U.S. EPA, 1980) because average body weight was known. A 50% absorption of the inhaled dose was assumed.

[c]Equivalent human doses were calculated by multiplying the transformed animal dose by the cube root of the ratio of animal body weight to reference human body weight (70 kg). Doses were divided by an uncertainty factor of 10 to approximate chronic exposure. This is equivalent to the animal dose scaled to the human dose by a surface area scaling factor (body weight $^{2/3}$) resulting in human equivalent dose.

[d]Calculated using 79 exposures, and then 82 exposures give the reported range (4.8509 and 5.0351 days/week).

[e]Estimated from growth curve

NR = Not reported

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TABLE 9-2

Inhalation Composite Scores for Bromochloromethane

Species	Animal Dose (mg/kg/day)	Chronic Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Rat	125.96	150.77	2.23	Increased relative organ weight (liver)	4	8.93	1000	Torkelson et al., 1960
Rat	170.14[b]	203.65	2.04	Liver histological alterations (bile duct epithelial proliferation, portal fibrosis, vacuolization)	6	12.22	1000	Torkelson et al., 1960
Rat	312.59	374.17	1.64	Increased hemosiderin in spleen	1	1.64	5000	Svirbely et al., 1947
Mouse	347.14[b]	183.21	2.11	Decreased body weight	4	8.42	1000	Torkelson et al., 1960
Guinea pig	262.10[b]	420.05	1.57	Testicular effects (decreased spermatogenesis in tubules with fibrosis)	6	9.39	1000	Torkelson et al., 1960
Dog	166.11	658.27	1.27	Kidney histological alterations (increased fat)	5	6.36	1000	Svirbely et al., 1947

[a]Human equivalent dose (mg/kg/day) from Table 9-1 multiplied by 70 kg to express MED in mg/day for a 70 kg human.

[b]Average of range reported in Table 9-1 (4.943 days/week)

(Table 9-3). This RQ is the same as a previously derived RQ (U.S. EPA, 1985), but the previous evaluation did not evaluate the studies by MacEwen et al. (1966) and Svirbely et al. (1947).

9.2. BASED ON CARCINOGENICITY

Pertinent data regarding the carcinogenicity of bromochloromethane to humans or animals by inhalation, oral or other routes of exposure were not located in the available literature cited in Appendix A. Because of the lack of carcinogenicity data, bromochloromethane is categorized in U.S. EPA weight-of-evidence Group D (Not Classifiable as to Human Carcinogenicity). Chemicals in EPA Group D are not ranked for cancer hazard or assigned cancer-based RQs.

TABLE 9-3

Bromochloromethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Species/Sex:	rat/female
Dose*:	203.65
Duration:	114 days (79-82 exposures, 7 hours/day)
Effect:	histological lesions in liver
RV_d:	2.04
RV_e:	6
CS:	12.22
RQ:	1000
Reference:	Torkelson et al., 1960

*Equivalent human dose

TABLE 9-3

Bromochloromethane

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Species/Sex:	rat/female
Dose*:	203.65
Duration:	114 days (79-82 exposures, 7 hours/day)
Effect:	histological lesions in liver
RV_d:	2.04
RV_e:	6
CS:	12.22
RQ:	1000
Reference:	Torkelson et al., 1960

*Equivalent human dose

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APPENDIX A

LITERATURE SEARCHED

This HEED is based on data identified by computerized literature searches of the following:

CHEMLINE
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
TOXLINE
TOXLIT
TOXLIT 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register
CAS ONLINE (Chemistry and Aquatic)
HSDB
SCISEARCH
Federal Research in Progress

These searches were conducted in April, 1989, and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 1987. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH with Intended Changes for 1987-1988. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

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McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

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APPENDIX B

Summary Table for Bromochloromethane

	Species	Exposure	Effect	RfD or q_1^*	Reference
Inhalation Exposure					
Subchronic	rat	370 ppm (1958 mg/m³), 7 hours/day for 135 exposures in 195 days (HEC = 395 mg/m³)	NOAEL for increased relative liver weight	4 mg/m³	Torkelson et al., 1960
Chronic	rat	370 ppm (1958 mg/m³), 7 hours/day for 135 exposures in 195 days (HEC = 395 mg/m³)	NOAEL for increased relative liver weight	0.4 mg/m³	Torkelson et al., 1960
Carcinogenicity	ID	ID	ID	ID	NA
Oral Exposure					
Subchronic	rat	370 ppm (1958 mg/m³), 7 hours/day for 135 exposures in 195 days† (126.0 mg/kg/day)	NOAEL for increased relative liver weight	1 mg/kg/day	Torkelson et al., 1960
Chronic	rat	370 ppm (1958 mg/m³), 7 hours/day for 135 exposures in 195 days† (126.0 mg/kg/day)	NOAEL for increased relative liver weight	0.1 mg/kg/day	Torkelson et al., 1960
Carcinogenicity	ID	ID	ID	ID	NA
REPORTABLE QUANTITIES					
Based on Chronic Toxicity:		1000			Torkelson et al., 1960
Based on Carcinogenicity:		ID			ID

†Inhalation exposure

ID = Insufficient data; NA = not applicable

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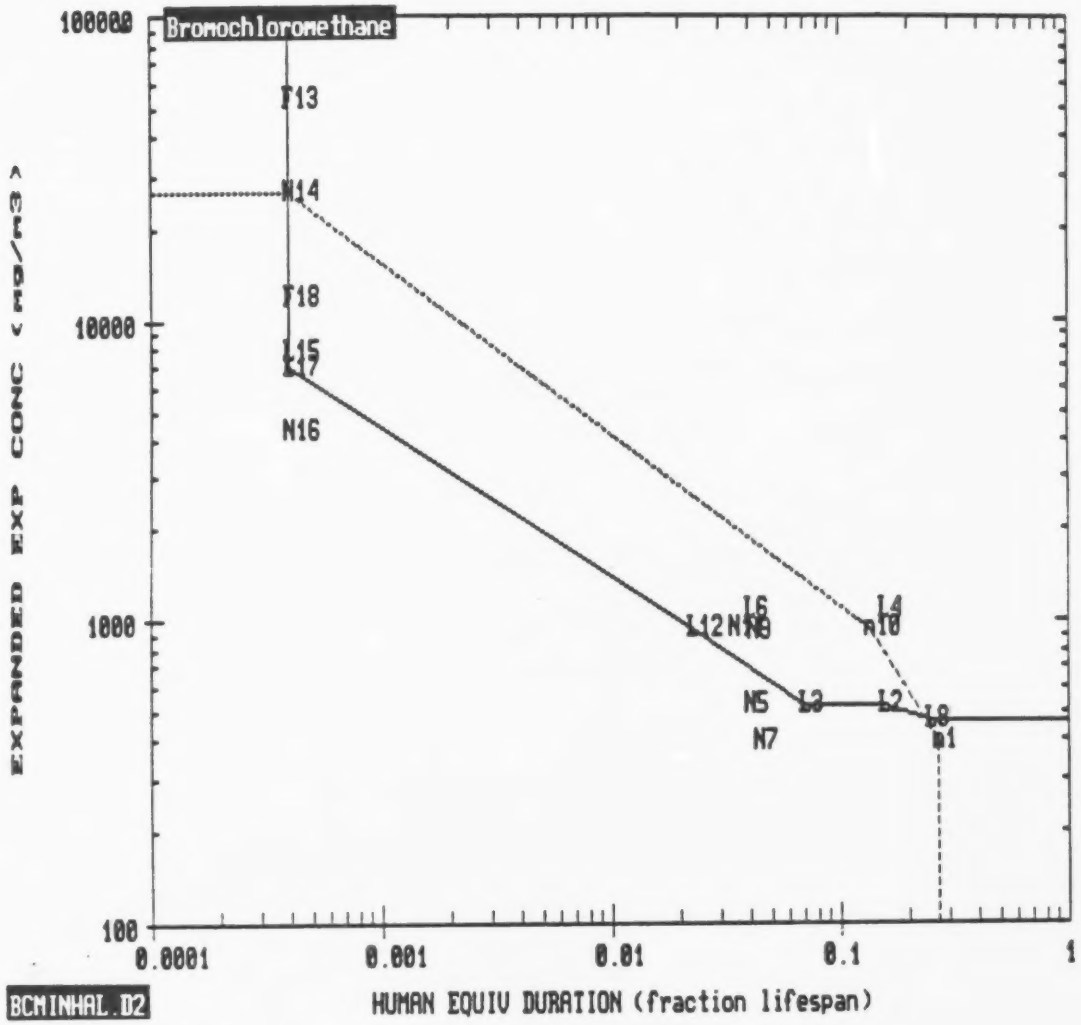
APPENDIX C

DOSE/DURATION RESPONSE GRAPHS FOR EXPOSURE TO BROMOCHLOROMETHANE

C.1. DISCUSSION

Dose/duration-response graphs for inhalation and oral exposure to bromochloromethane generated by the method of Crockett et al. (1985) using the computer software by Durkin and Meylan (1989) developed under contract to ECAO-Cincinnati are presented in Figures C-1 to C-6. Data used to generate these graphs are presented in Section C.2. In the generation of these figures, all responses are classified as adverse (FEL, AEL or LOAEL) or nonadverse (NOEL or NOAEL) for plotting. The ordinate expresses inhalation exposure in either of two ways. In Figures C-1 and C-2, the experimental concentration, expressed as mg/m^3, was multiplied by the time parameters of the exposure protocol (e.g., hours/day and days/week), and is presented as expanded experimental concentration [expanded exp conc (mg/m^3)]. In Figures C-3 and C-4, the expanded experimental concentration was multiplied by the animal inhalation rate in m^3/day and divided by the animal body weight in kg to calculate a daily dose in mg/kg/day. The daily dose was then multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in metabolic rate (Mantel and Schneiderman, 1975). The result was multiplied by an absorption coefficient of 0.5 to adjust to an equivalent absorbed dose and then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human [human equiv dose (mg/day)]. For oral exposure, the ordinate expresses dose as human equivalent dose. The animal dose, in mg/kg/day, is multiplied by the cube root of the ratio of the animal:human body weight to adjust for species differences in basal metabolic rate

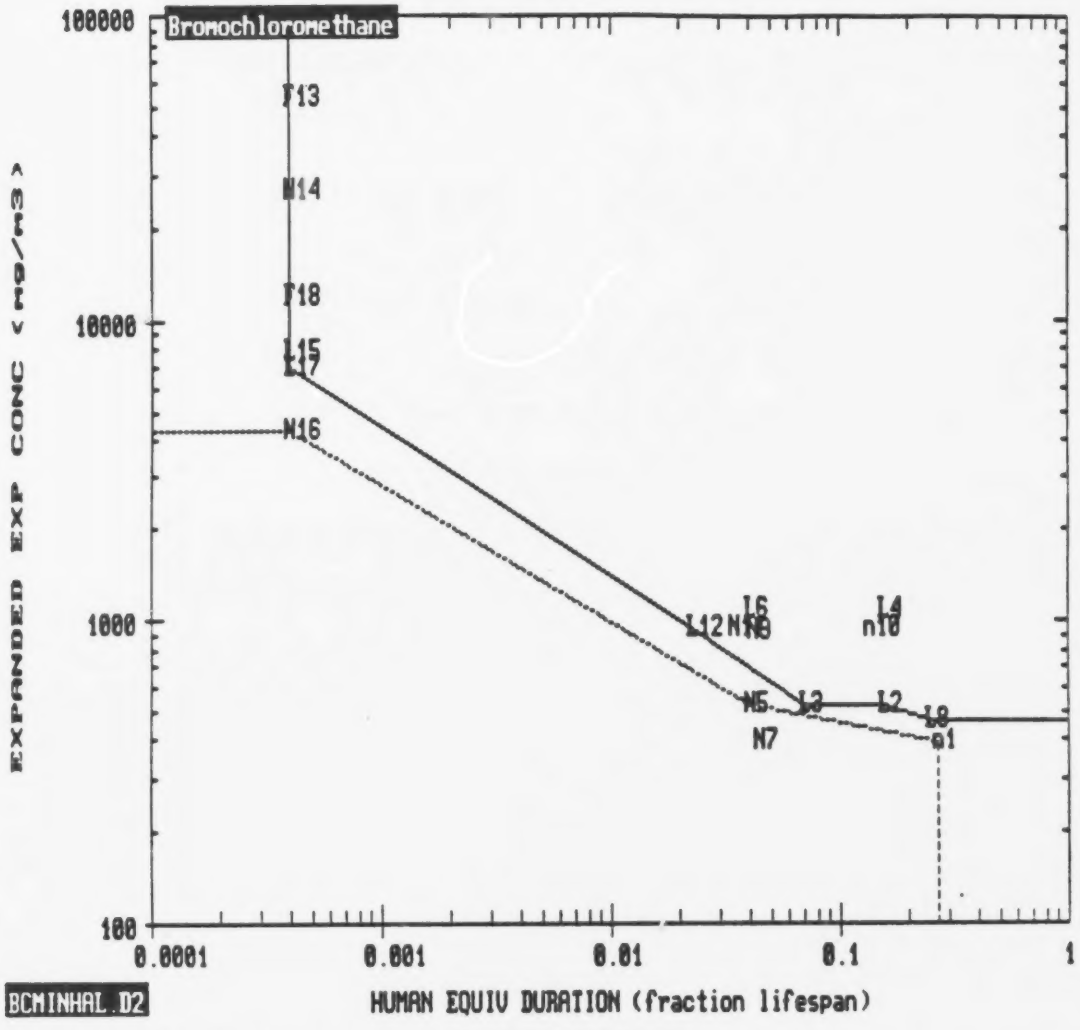


Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-1

Dose/Duration - Response Graph for Inhalation Exposure to Bromochloromethane: Envelope Method (Expanded Experimental Concentration)

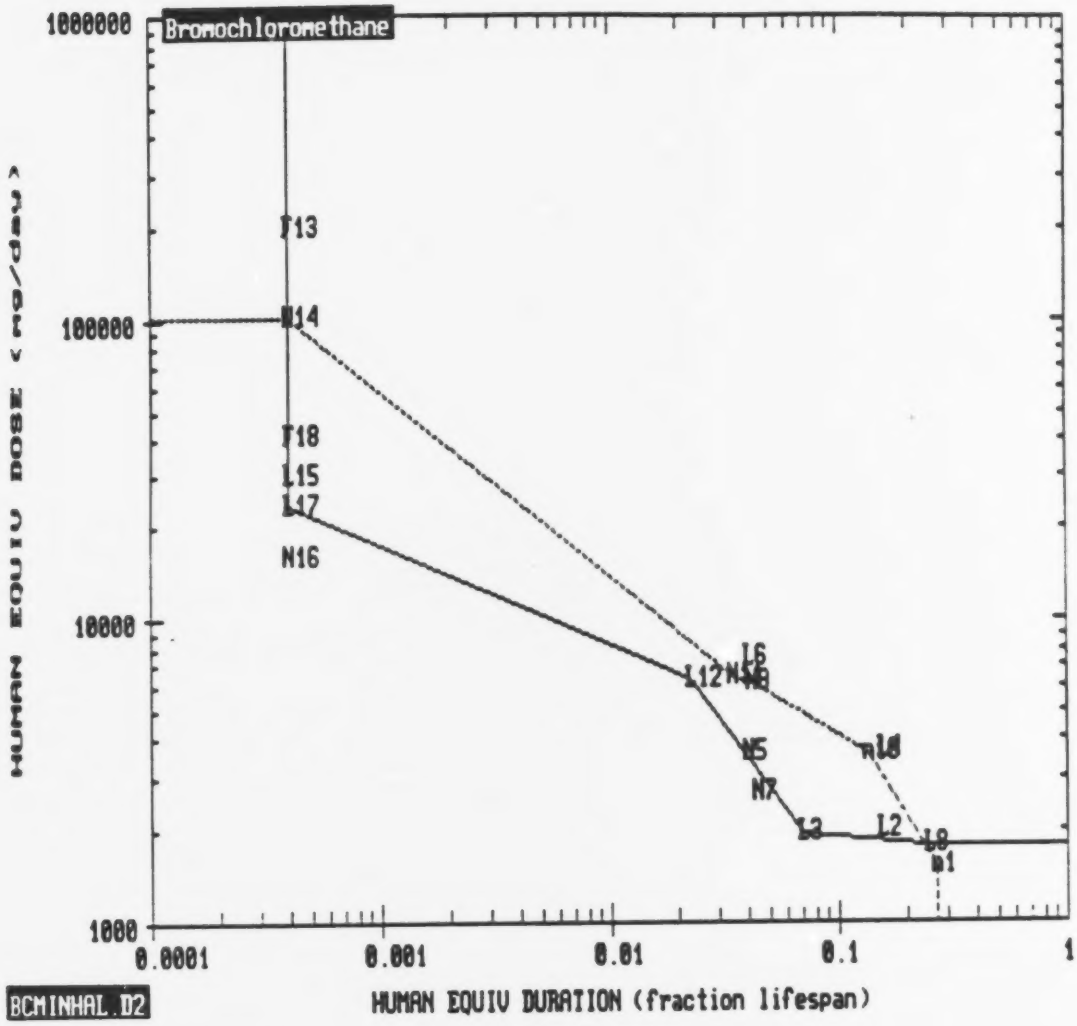


Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-2

Dose/Duration - Response Graph for Inhalation Exposure to Bromochloromethane: Censored Data Method (Expanded Experimental Concentration)

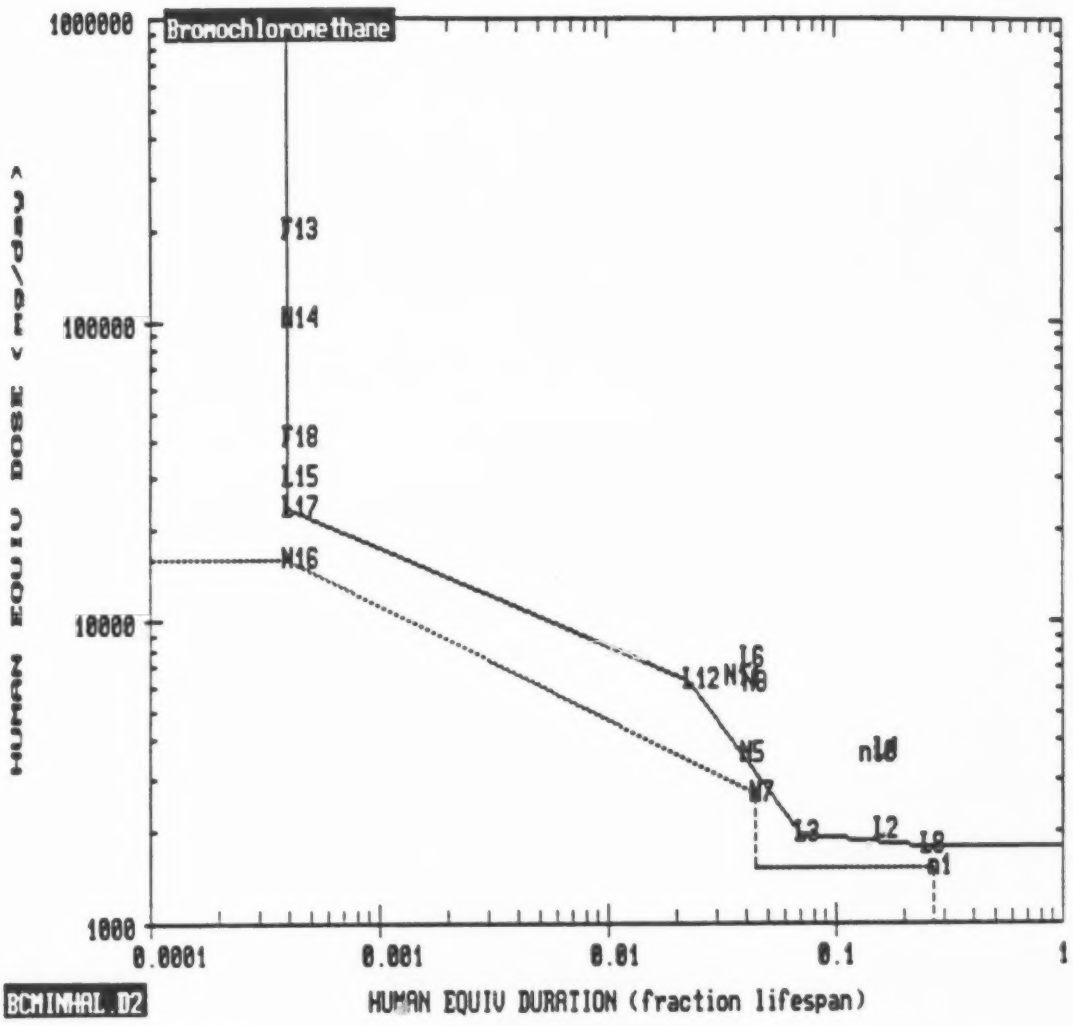


Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-3

Dose/Duration - Response Graph for Inhalation Exposure to Bromochloromethane: Envelope Method (Human Equivalent Dose)

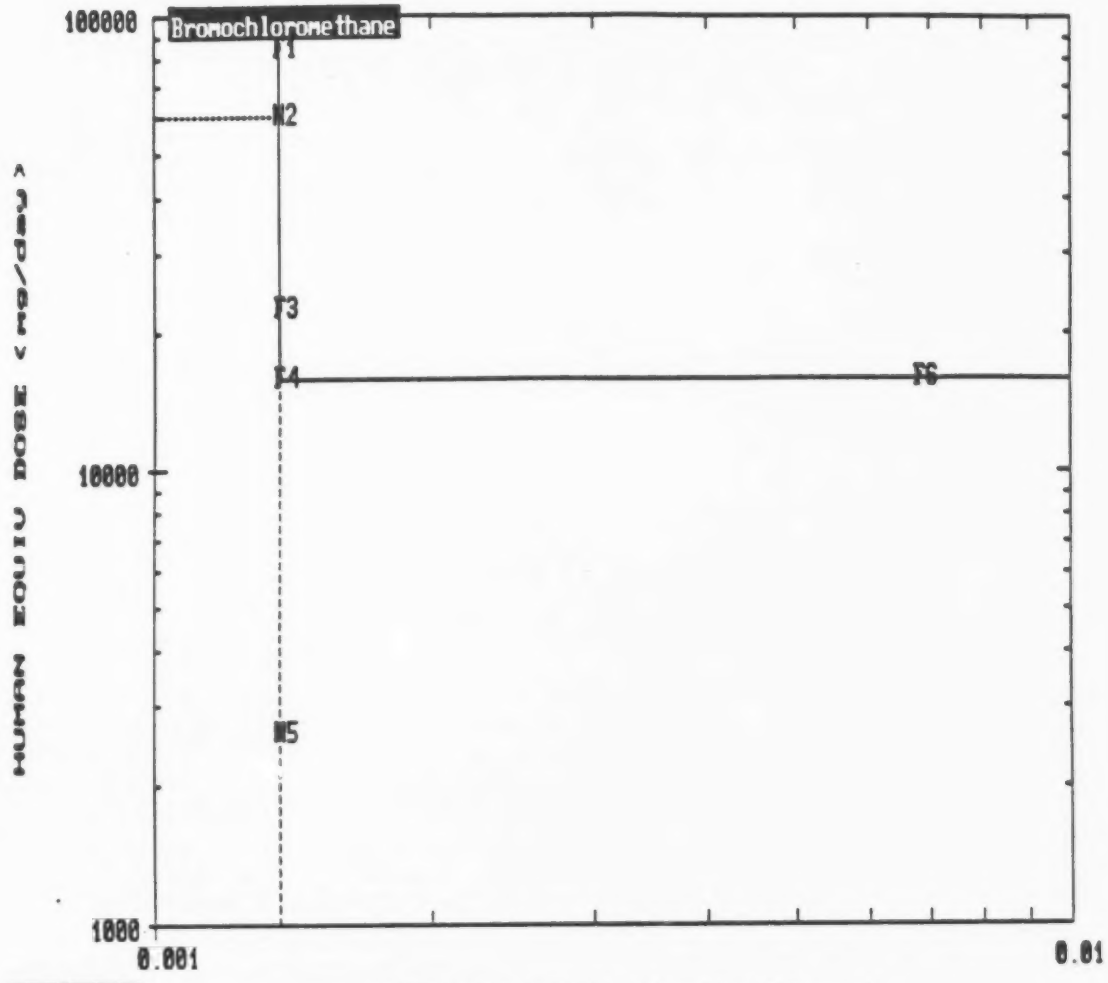


Key: F = FEL
L = LOAEL
n = NOAEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-4

Dose/Duration - Response Graph for Inhalation Exposure to Bromochloromethane: Censored Data Method (Human Equivalent Dose)

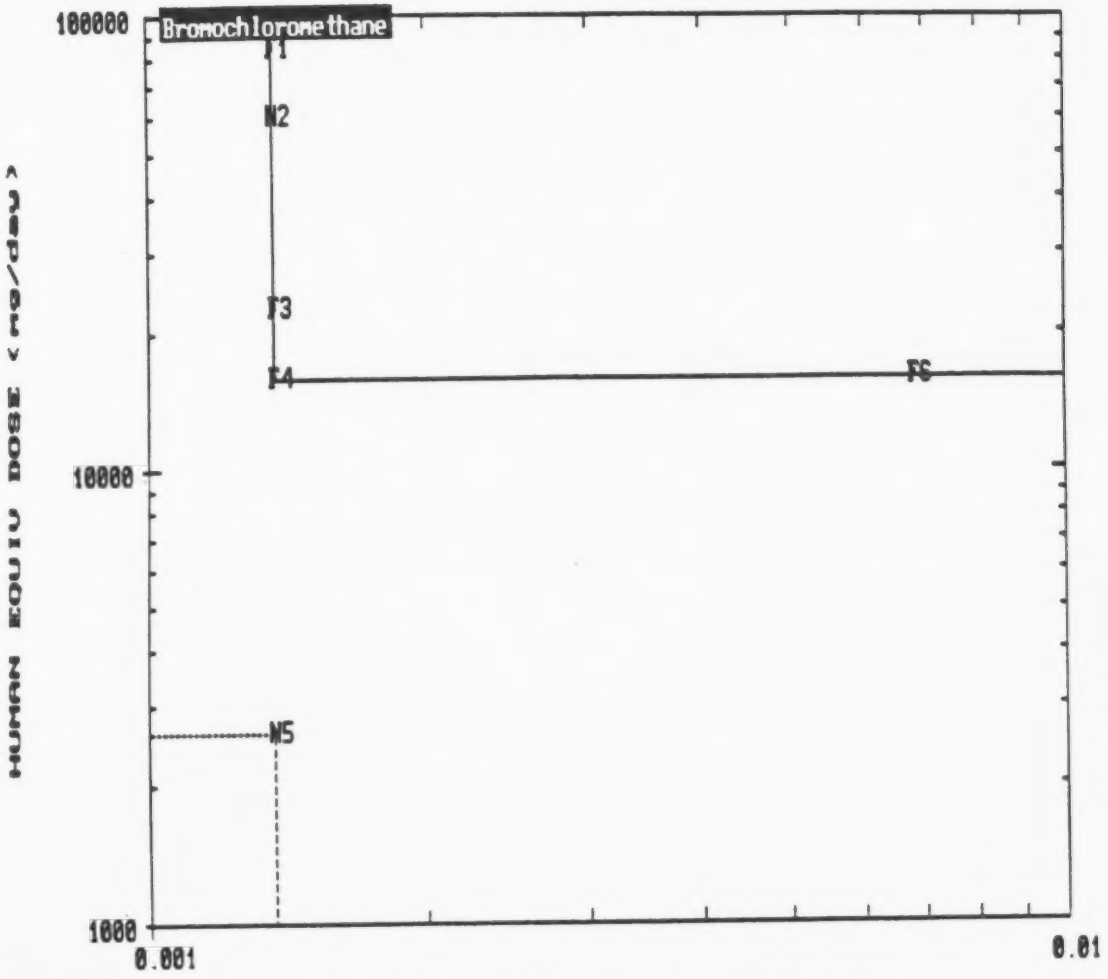


Key: F = FEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-5

Dose/Duration - Response Graph for Oral Exposure to Bromochloromethane: Envelope Method



Key: F = FEL
N = NOEL

Solid line = Adverse Effects Boundary
Dashed line = No Adverse Effects Boundary

FIGURE C-6

Dose/Duration - Response Graph for Oral Exposure to Bromochloromethane: Censored Data Method

(Mantel and Schneiderman, 1975). The result is then multiplied by 70 kg, the reference human body weight, to express the human equivalent dose as mg/day for a 70 kg human [human equiv dose (mg/day)].

The adverse effects boundary (solid line) is drawn by identifying the lowest adverse effect dose or concentration at the shortest duration of exposure at which an adverse effect occurred. From this starting point, an infinite line is extended upward, parallel to the dose axis. The starting point is then connected to the lowest adverse effect dose or concentration at the next longer duration of exposure that has an adverse effect dose or concentration equal to or lower than the previous one. This process is continued to the lowest adverse effect dose or concentration. From this point, a line parallel to the duration axis is extended infinitely to the right. The adverse effects region lies above the adverse effects boundary.

Using the envelope method, the no adverse effects boundary (dashed line) is drawn starting with the point representing the highest no adverse effects dose or concentration. From this point, a line parallel to the duration axis is extended to the dose or concentration axis. The starting point is then connected to the next equal or lower no adverse effect dose or concentration at a longer duration of exposure. When this process can no longer be continued, a line parallel to the dose or concentration axis is dropped to the duration axis. The no adverse effects region lies below the no adverse effects boundary. At either ends of the graph between the adverse effects and no adverse effects boundaries are regions of ambiguity. The area (if any) resulting from intersections of the adverse effects and no adverse effects boundaries is defined as the region of contradiction.

In the censored data method, all no adverse effect points located in the region of contradiction are dropped from consideration and the no adverse effects boundary is redrawn so that it does not intersect the adverse

effects boundary, and no region of contradiction is generated. This method results in the most conservative definition of the no adverse effects region.

Figures C-1 and C-3 present the inhalation dose/duration-response graphs generated by the envelope method. The adverse effects boundary is defined by the LOAEL for liver histological alterations in mice (Rec. #17), LOAELs for kidney histological alterations in dogs (Rec. #12), reduced body weight and elevated organ weights in guinea pigs (Rec. #3), liver histological alterations in rats (Rec. #2) and for reduced body weight in rats (Rec. #8). Using the envelope method (Figures C-1 and C-4), the no adverse effects boundary is defined by the acute NOEL for mortality in rats (Rec. #14), a NOAEL for slightly increased hemosiderin in the spleen of rats (Rec. #10) and a NOAEL for increased liver weight in rats (Rec. #1). Using the censored data method (Figures C-2 and C-4), the no adverse effects boundary is defined by the NOEL for liver histological alterations in rats (Rec. #16), the NOEL in rabbits (Figure C-2, Rec. #5) or dogs (Figure C-4, Rec. #7) and the NOAEL for liver histological alterations in rats (Rec. #1). The subchronic and chronic RfDs for bromochloromethane are based on the NOAEL for liver histological alterations in rats (Rec. #1).

Figures C-5 and C-6 present the oral dose/duration-response graphs. The adverse effects boundary is defined by FELs for mortality in rats (Rec. #1) and mortality in mice (Recs. #3, 4 and 6). In Figure C-5 (envelope method), the no adverse effects boundary is defined by the NOEL for mortality in rats (Rec. #2) and the NOEL for mortality and histopathology in mice (Rec. #5). Using the censored data method (Figure C-6), the no adverse effects boundary is defined by a single value, the NOEL for mortality and histopathology in mice (Rec. #5). Figures C-5 and C-6 emphasize that additional oral data (i.e., for longer duration exposures) are needed to identify a maximal region of no adverse effects.

C.2. DATA USED TO GENERATE DOSE/DURATION-RESPONSE GRAPHS

C.2.1. Inhalation Exposure.

Chemical Name: Bromochloromethane
CAS Number: 74-97-5
Document Title: Health and Environmental Effects Document on Bromochloromethane
Document Number: Pending
Document Date: Pending
Document Type: HEED

RECORD #1:

Species: Rats
Sex: Female
Effect: NOAEL
Route: Inhalation

Body Weight: 0.35 kg
Reported Dose: 1958 mg/m³
Converted Dose: 125.96 mg/kg/day
Exposure Period: 195 days
Duration Observation: 195 days

Molecular Weight: 129.39
Inhalation hours/day: 7.00
Inhalation days/week: 4.8461
Inhal. Exp. days: 135.00
Assumed Inhalation Absorption: 50%

Number Exposed: 10
Number Responses: NR
Type of Effect: WGTIN
Site of Effect: LIVER
Severity Effect: 4

Comment: Concentrations studied: 1958, 2593 and 5345 mg/m³ (370, 490 and 1010 ppm or 125.96, ~170.14, ~350.69 mg/kg/day). Both sexes treated at higher concentrations. No effects on histology, hematology, blood nitrogen or body weight.

Citation: Torkelson et al., 1960

RECORD #2:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Both	Reported Dose:	2593 mg/m³
Effect:	LOAEL	Converted Dose:	166.97-173.31 mg/kg/day
Route:	Inhalation	Exposure Period:	114 days
		Duration Observation:	114 days
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.8509-5.0351
		Inhal. Exp. days:	79.00-82.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	40
Number Responses:	NR
Type of Effect:	PROLF
Site of Effect:	LIVER
Severity Effect:	5

Comment: 20/sex, 79-82 exposures. See previous record. Effects included slight bile duct proliferation, slight portal fibrosis and occasional vacuolization. Similar effects with cloudy swelling in liver in both sexes at 5345 mg/m³ (344.18-357.25 mg/kg/day).

Citation: Torkelson et al., 1960

RECORD #3:

Species:	Guinea pigs	Body Weight:	0.84 kg
Sex:	Both	Reported Dose:	2593 mg/m³
Effect:	LOAEL	Converted Dose:	124.29-129.53 mg/kg/day
Route:	Inhalation	Exposure Period:	114 days
		Duration Observation:	114 days
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.8509-5.0351
		Inhal. Exp. days:	79.00-82.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	20	20	20
Number Responses:	NR	NR	NR
Type of Effect:	WGTIN	WGTIN	WGTDC
Site of Effect:	LIVER	KIDNY	BODY
Severity Effect:	4	4	4

Comment: 10/sex, 79-82 exposures. Exposure concentrations: 2593 and 5345 mg/m³ (490 and 1010 ppm). Effect on kidney weight only in males. No effects on histology or blood nitrogen. Testicular effects (decreased weight, spermatogenesis) at 5345 mg/m³ (257.23-267.00 mg/kg/day).

Citation: Torkelson et al., 1960

RECORD #4:

Species:	Mice
Sex:	Female
Effect:	LOAEL
Route:	Inhalation

Body Weight: 0.03 kg
Reported Dose: 5345 mg/m³
Converted Dose: 702.22-728.88 mg/kg/day
Exposure Period: 114 days
Duration Observation: 114 days

Molecular Weight: 129.39
Inhalation hours/day: 7.00
Inhalation days/week: 4.8509-5.0351
Inhal. Exp. days: 79.00-82.00
Assumed Inhalation Absorption: 50%

Number Exposed:	10	10	10
Number Responses:	NR	NR	NR
Type of Effect:	WGTDC	WGTIN	WGTIN
Site of Effect:	BODY	LIVER	KIDNY
Severity Effect:	4	4	4

Comment: 79-82 exposures. Exposure concentrations: 2593 and 5345 mg/m³ (490 and 1010 ppm) (340.67-353.59 and 702.22-728.88 mg/kg/day). Same effects at 2593 mg/m³. No effects on histology. Other endpoints not examined.

Citation: Torkelson et al., 1960

RECORD #5:

Species:	Rabbits
Sex:	Both
Effect:	NOEL
Route:	Inhalation

Body Weight: 3.8 kg
Reported Dose: 2593 mg/m³
Converted Dose: 137.93-143.16 mg/kg/day
Exposure Period: 114 days
Duration Observation: 114 days

Molecular Weight: 129.39
Inhalation hours/day: 7.00
Inhalation days/week: 4.8509-5.0351
Inhal. Exp. days: 79.00-82.00
Assumed Absorption Inhalation: 50%

Number Exposed:	4
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	3

Comment: 2/sex, 79-82 exposures. Exposure concentrations: 2593 and 5345 mg/m³ (490 and 1010 ppm) (137.93-143.16 and 284.32-295.09 mg/kg/day, respectively). No effects on histology, organ weight, body weight or blood nitrogen.

Citation: Torkelson et al., 1960

RECORD #6:

Species:	Rabbits	Body Weight:	3.8 kg
Sex:	Male	Reported Dose:	5345 mg/m³
Effect:	LOAEL	Converted Dose:	284.29-295.09 mg/kg/day
Route:	Inhalation	Exposure Period:	114 days
		Duration Observation:	114 days
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.8509-5.0351
		Inhal. Exp. days:	79.00-82.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	2
Number Responses:	1
Type of Effect:	DEGEN
Site of Effect:	TESTE
Severity Effect:	6

Comment: See previous record. Decreased spermatogenesis in tubules with fibrosis in 1 of 2 males. Decreased relative testes weight.

Citation: Torkelson et al., 1960

RECORD #7:

Species:	Dogs	Body Weight:	12.7 kg
Sex:	Both	Reported Dose:	1958 mg/m³
Effect:	NOEL	Converted Dose:	66.93 mg/kg/day
Route:	Inhalation	Exposure Period:	195 days
		Duration Observation:	195 days
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.8462
		Inhal. Exp. days:	135.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	2
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	4

Comment: 1/sex. 370 ppm equivalent concentration. No effect on body weight, blood nitrogen or hematology. Pathological examinations not performed.

Citation: Torkelson et al., 1960

RECORD #8:

Species:	Rats	Body Weight:	0.32 kg
Sex:	Both	Reported Dose:	2725 mg/m³
Effect:	LOAEL	Converted Dose:	149.51 mg/kg/day
Route:	Inhalation	Exposure Period:	6 months
		Duration Observation:	6 months
		Molecular Weight:	129.39
		Inhalation hours/day:	6.00
		Inhalation days/week:	4.8222
		Inhal. Exp. days:	124.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	100
Number Responses:	NR
Type of Effect:	WGTDC
Site of Effect:	BODY
Severity Effect:	4

Comment: 50/sex. Exposure concentrations: 2725 and 5345 mg/m³ (515 and 1010 ppm) (149.51 and 293.26 mg/kg/day, respectively). No effect on body weight in females. No effect on histology, organ weights or clinical chemistry at either exposure level.

Citation: MacEwen et al., 1966

RECORD #9:

Species:	Dogs	Body Weight:	12.7 kg
Sex:	Both	Reported Dose:	5345 mg/m³
Effect:	NOEL	Converted Dose:	155.84 mg/kg/day
Route:	Inhalation	Exposure Period:	6 months
		Duration Observation:	6 months
		Molecular Weight:	129.39
		Inhalation hours/day:	6.00
		Inhalation days/week:	4.8222
		Inhal. Exp. days:	124.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	8
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	3

Comment: 4/sex. Dogs were exposed to 0, 515 or 1010 ppm (2725 or 5345 mg/m³) bromochloromethane (79.45 and 155.84 mg/kg/day, respectively). No effect on body weight, organ weight, histology or clinical chemistry.

Citation: MacEwen et al., 1966

RECORD #10:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Male	Reported Dose:	4710 mg/m³
Effect:	NOAEL	Converted Dose:	299.20 mg/kg/day
Route:	Inhalation	Exposure Period:	14 weeks
		Duration Observation:	14 weeks
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.7857
		Inhal. Exp. days:	67.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	20
Number Responses:	NR
Type of Effect:	OTHER
Site of Effect:	SPLEN
Severity Effect:	1

Comment: 890 ppm equivalent concentration. Histology was evaluated after 67 exposures. Increased hemosiderin in spleen. No other effect on histology or weight gain. Other endpoints not evaluated.

Citation: Svirbely et al., 1947

RECORD #11:

Species:	Rabbits	Body Weight:	3.8 kg
Sex:	Male	Reported Dose:	4710 mg/m³
Effect:	NOEL	Converted Dose:	247.16 mg/kg/day
Route:	Inhalation	Exposure Period:	14 weeks
		Duration Observation:	14 weeks
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.7857
		Inhal. Exp. days:	67.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	3
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	3

Comment: Exposure concentration is equivalent to 830 ppm. Histology evaluated after 67 days. No effect on histology, weight gain, hematology, liver function or urinalysis.

Citation: Svirbely et al., 1947

RECORD #12:

Species:	Dogs	Body Weight:	12.7 kg
Sex:	Female	Reported Dose:	4710 mg/m³
Effect:	LOAEL	Converted Dose:	158.99 mg/kg/day
Route:	Inhalation	Exposure Period:	14 weeks
		Duration Observation:	14 weeks
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	4.7857
		Inhal. Exp. days:	67.00
		Assumed Inhalation Absorption:	50%

Number Exposed:	2
Number Responses:	NR
Type of Effect:	DEGEN
Site of Effect:	KIDNY
Severity Effect:	5

Comment: 890 ppm equivalent concentration. Histology was evaluated after 67 exposures. Increased fat in the kidneys and increased hemosiderin in the kidneys and spleen. No effect on weight gain, hematology, liver function or urinalysis.

Citation: Svirbely et al., 1947

RECORD #13:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Both	Reported Dose:	10000 ppm
Effect:	FEL	Converted Dose:	702.45 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	14 days
		Molecular Weight:	129.39
		Inhalation hours/day:	7.00
		Inhalation days/week:	1.00
		# Inhal. Exp. days:	
		Assumed Inhalation Absorption:	50%

Number Exposed:	20
Number Responses:	11
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Single 7-hour exposure. Concentration not expanded over 24 hours. 6/10 males and 5/10 females died. Deaths generally occurred during exposure to anesthesia.

Citation: Torkelson et al., 1960

RECORD #14:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Both	Reported Dose:	5000 ppm
Effect:	NOEL	Converted Dose:	351.23 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	14 days
		Molecular Weight:	
		Inhalation hours/day:	7.00
		Inhalation days/week:	1.00
		# Inhal. Exp. days:	
		Assumed Inhalation Absorption:	50%

Number Exposed:	22
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	10

Comment: Single 7-hour exposure. Concentration not expanded over 24 hours. 0/11 males and 0/11 females died.

Citation: Torkelson et al., 1960

RECORD #15:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Female	Reported Dose:	1500 ppm
Effect:	LOAEL	Converted Dose:	105.37 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	1 day
		Molecular Weight:	
		Inhalation hours/day:	7.00
		Inhalation days/week:	1.00
		# Inhal. Exp. days:	
		Assumed Inhalation Absorption:	50%

Number Exposed:	4
Number Responses:	NR
Type of Effect:	DEGEN
Site of Effect:	LIVER
Severity Effect:	5

Comment: Minimum concentration producing unequivocal hepatic effects 24 hours after 7-hour exposure. Concentration not expanded over 24 hours. Effects included small vacuoles not typical of fatty degeneration often accompanied by increased liver weight.

Citation: Torkelson et al., 1960

RECORD #16:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Female	Reported Dose:	600 ppm
Effect:	NOEL	Converted Dose:	42.15 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	1 day
		Molecular Weight:	
		Inhalation hours/day:	7.00
		Inhalation days/week:	1.00
		# Inhal. Exp. days:	
		Assumed Inhalation Absorption:	50%

Number Exposed:	4
Number Responses:	NR
Type of Effect:	
Site of Effect:	
Severity Effect:	3

Comment: Maximum concentration that did not produce hepatic histological effects 24 hours after a single 7-hour exposure. Concentration not expanded over 24 hours.

Citation: Torkelson et al., 1960

RECORD #17:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	7 mg/ℓ
Effect:	LOAEL	Converted Dose:	189.62 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	1 day
		Molecular Weight:	
		Inhalation hours/day:	7.00
		Inhalation days/week:	1.00
		# Inhal. Exp. days:	
		Assumed Inhalation Absorption:	50%

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEGEN
Site of Effect:	LIVER
Severity Effect:	5

Comment: Single 7-hour exposure. 1323 ppm equivalent concentration. Concentration not expanded over 24 hours. Fatty degeneration. Effect observed in mice exposed to concentrations of 7-17 mg/m^3 for 1-5 days but was minimal/absent after 72 hours.

Citation: Highman et al., 1948

RECORD #18:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	2273 ppm
Effect:	FEL	Converted Dose:	325.78 mg/kg/day
Route:	Inhalation	Exposure Period:	0.29 days
		Duration Observation:	6 days

Molecular Weight:
Inhalation hours/day: 7.00
Inhalation days/week: 1.00
Inhal. Exp. days:
Assumed Inhalation Absorption: 50%

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Concentration not expanded over 24 hours. LC_{50} after 72-hour observation. A similar value was reported by Highman et al. (1948). LC_{50}s after 8, 24 and 48 hours observation were 2995, 2504 and 2436 ppm, respectively.

Citation: Svirbely et al., 1947

C.2.2. Oral Exposure.

Chemical Name: Bromochloromethane
CAS Number: 74-97-5
Document Title: Health and Environmental Effects Document on Bromochloromethane
Document Number: Pending
Document Date: Pending
Document Type: HEED

RECORD #1:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Male	Reported Dose:	7000 mg/kg/dav
Effect:	FEL	Converted Dose:	7000 mg/kg/day
Route:	Gavage	Exposure Period:	1 day
		DurationObservation:	1 day

Number Exposed:	5
Number Responses:	5
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: All rats died within 24 hours of treatment. Dose administered in corn oil apparently by gavage.

Citation: Torkelson et al., 1960

RECORD #2:

Species:	Rats	Body Weight:	0.35 kg
Sex:	Male	Reported Dose:	5000 mg/kg/day
Effect:	NOEL	Converted Dose:	5000 mg/kg/day
Route:	Gavage	Exposure Period:	1 day
		Duration Observation:	14 days

Number Exposed:	5
Number Responses:	0
Type of Effect:	
Site of Effect:	
Severity Effect:	10

Comment: No deaths. See previous record.

Citation: Torkelson et al., 1960

RECORD #3:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	4300 mg/kg/day
Effect:	FEL	Converted Dose:	4300 mg/kg/day
Route:	Gavage	Exposure Period:	1 day
		Duration Observation:	6 days

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Approximate LD_{50}. Doses ranging from 500-4400 mg/kg/day administered in corn oil apparently by gavage to groups of 10 animals.

Citation: Svirbely et al., 1947

RECORD #4:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	3000 mg/kg/day
Effect:	FEL	Converted Dose:	3000 mg/kg/day
Route:	Gavage	Exposure Period:	1 day
		Duration Observation:	12 days

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Single doses of 500, 3000 and 4500 mg/kg were administered in corn oil. 12/50 mice that died or were killed at two highest doses showed subcapsular necrosis in liver. 8/32 showed hemoglobin casts in renal tubules.

Citation: Higman et al., 1948

RECORD #5:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	500 mg/kg/day
Effect:	NOEL	Converted Dose:	500 mg/kg/day
Route:	Gavage	Exposure Period:	1 day
		Duration Observation:	12 days

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	
Site of Effect:	
Severity Effect:	3

Comment: See previous record. No effect on mortality or histology.

Citation: Highman et al., 1948

RECORD #6:

Species:	Mice	Body Weight:	0.03 kg
Sex:	NR	Reported Dose:	3000 mg/kg/day
Effect:	FEL	Converted Dose:	3000 mg/kg/day
Rout:e	Gavage	Exposure Period:	5 days
		Duration Observation:	5 days

Number Exposed:	NR
Number Responses:	NR
Type of Effect:	DEATH
Site of Effect:	BODY
Severity Effect:	10

Comment: Death in unspecified number of 32 mice that were given single doses in olive oil on 1 to 10 consecutive days. Histologic examination showed effects including fatty degeneration of the liver and kidney and liver subcapsular necrosis.

Citation: Highman et al., 1948

NR = Not reported